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CONGENITAL ANOMALIES OF THE ESOPHAGUS RELATED TO ESOPHAGEAL FOREIGN BODIES

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ATTENTION has recently been sharply focused on congenital lesions of the esophagus. This is because of the fact that surgical repair of the atresias is now possible, whereas formerly they were invariably fatal. Congenital anomalies of the esophagus, other than complete atresia, are apparently less well known and understood, but they undoubtedly occur more frequently than is generally recognized. They manifest their presence by signs and symptoms of dysphagia, often insidious and slowly progressive but occasionally dramatically apparent as a foreign body becomes lodged in the lesion to produce sudden partial or complete esophageal obstruction. In such instances, the episode of the foreign body assumes major importance and the underlying congenital esophageal stenosis may not be recognized and its significance not understood.

This paper is an analysis of cases of foreign bodies in the esophagus in which the lodgment of the foreign body was due to a congenital anomaly of the esophagus. The types of congenital esophageal stenoses are discussed, with suggestions regarding their diagnosis and treatment.

REPORT OF CASES

CASE 1.—J. N., a 4 year old girl had swallowed a penny; roentgenograms demonstrated it to be in the lower thoracic portion of the esophagus. A history was obtained of difficulty in swallowing since infancy; all fluids were taken eagerly and without difficulty, but soft and solid foods were not swallowed easily, and there were frequent episodes of complete inability to swallow associated with drooling of saliva. Some time previously a foreign body had been removed elsewhere, following which roentgenograms had demonstrated a typical congenitally short esophagus. The penny was extracted, and following the extraction another esophagoscopic examination was made which demonstrated the characteristic tight stricture above the level of the diaphragm seen in the congenitally short

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esophagus. The esophagoscope was passed through the strictured area into the supradiaphragmatic portion of the stomach. Several more dilations were necessary to improve the child's swallowing function.

CASE 2.—L. N., a 2½ year old boy, swallowed three pennies. Roentgenograms demonstrated these to be present in the lower portion of the esophagus. The anteroposterior view showed a single coin, and the lateral view showed what appeared to be three separate coins superimposed in the distal part of the esophagus (fig. 1). These were removed by means of a forward-grasping forceps passed through a 7 mm. by 30 cm. standard esophagoscope. Subsequent discussion with the patient's family revealed the fact that the child had had difficulty in swallowing solid food since birth. Roentgenograms demonstrated a typical congenitally short esophagus (fig. 2) which was subsequently dilated, with relief of persistent dysphagia.

CASE 3.—L. B., a boy was 6 years old when first seen. He had had frequent attacks of vomiting of recently swallowed food for the past five years. His development was otherwise normal, and he had had the usual childhood diseases.

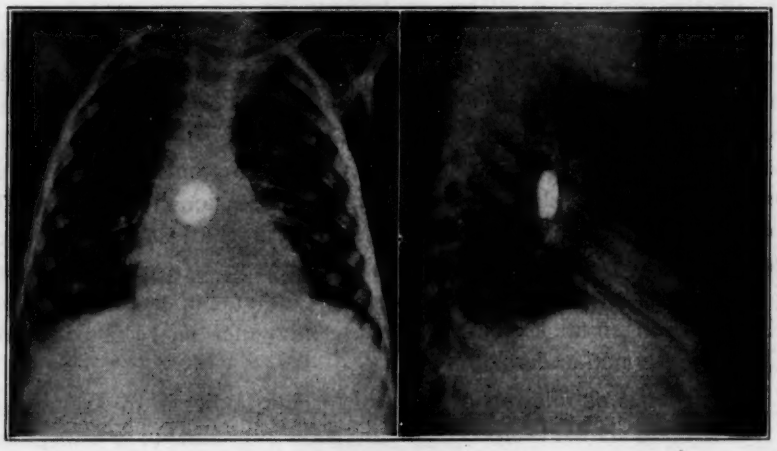

Fig. 1 (case 2).—Anteroposterior and lateral roentgenograms of the chest showing three pennies superimposed in the distal portion of the esophagus.

When still an infant, he learned to vomit with little effort the food he had swallowed, and this was noted particularly when he was given solid or coarse foods. Liquids and soft foods were tolerated quite well. At various times he would lose weight, depending on the severity of the emeses. He had been treated for anemia on several occasions. Prior to his present admission to the hospital he had had fewer periods during which he could swallow satisfactorily and the vomiting was severer and more frequent, occurring after almost every meal. The mother had noted that rarely were stomach contents seen in the vomited material. Fluoroscopic examination showed the upper portion of the esophagus to be considerably dilated, the distal third to be decidedly constricted. The barium sulfate only trickled through the distal third of the esophagus. Esophagoscopic examination showed a large quantity of undigested food in the upper thoracic part of the esophagus. At a point 24 cm. from the upper teeth a piece of undigested food, apparently meat, was found impacted in a tight stricture. There was a zone of inflammation around the stenosis, and only small bougies could be passed through the

constricted area into the stomach. By dilation with the lip of the esophagoscope, the instrument was gradually advanced through the stricture into the stomach itself. The stricture appeared to be 3 to 4 cm. in length and its walls inflamed and covered with granulation tissue. Repeated dilations since that time have been carried out at various intervals, depending on the child's swallowing function. Dilations are followed by definite improvement. The child was first seen in December 1941; dilations were carried out intermittently until July 1945, when the esophagoscope could be passed through the area without resistance and the walls were found to be smooth.

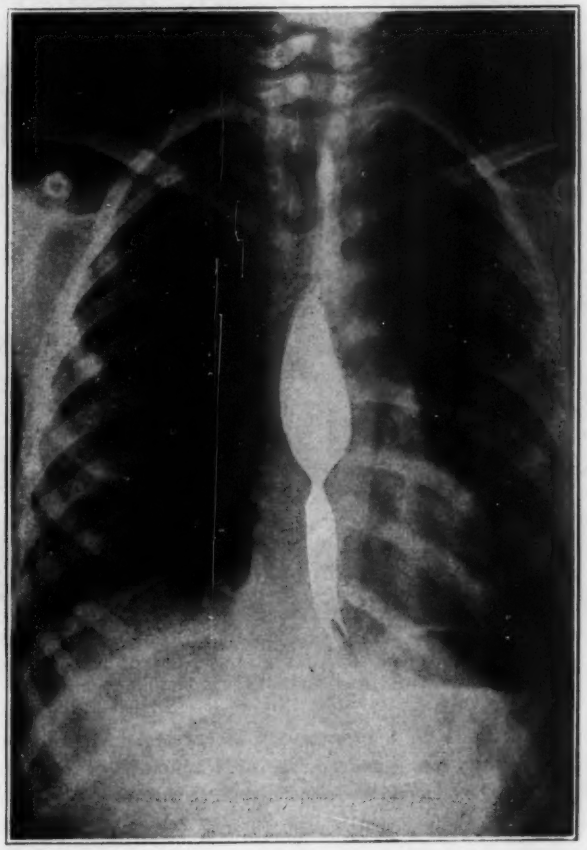

Fig. 2 (case 2).—Esophagram showing a typical congenitally short esophagus. This film was made following the removal of the three pennies shown in figure 1.

CASE 4.—B. P., a boy 6 years of age, swallowed a pebble which became lodged in what was thought to be the midthoracic portion of the esophagus. After the pebble was removed, fluoroscopic examination of the esophagus was made and results were reported as follows:

After administration of the barium sulfate, the compound proceeded to pass without difficulty into the upper two thirds of the esophagus. In the lower third of the esophagus, however, there was a definite retardation. Fluoroscopically, it was noted that the lower portion of the esophagus for a distance of about 2½

inches (6.4 cm.) was considerably narrowed and above this narrowed area there was a compensatory dilatation of the esophagus. This narrowing of the lower portion of the esophagus was constant on fluoroscopic examination, as well as on the roentgenograms that were taken later. However, the outline of the narrow part of the esophagus was quite smooth.

Findings were suggestive of a benign stricture of the lower portion of the esophagus. There was no history of ingestion of a caustic material. The esophagoscopic examination showed an extremely inflamed tight stricture in the midportion of the esophagus surrounded by granulation tissue. The response to dilation was rapid, and it was possible to pass a 7 mm. standard esophagoscope through the stricture into the stomach with relatively few dilations. Dilations were carried

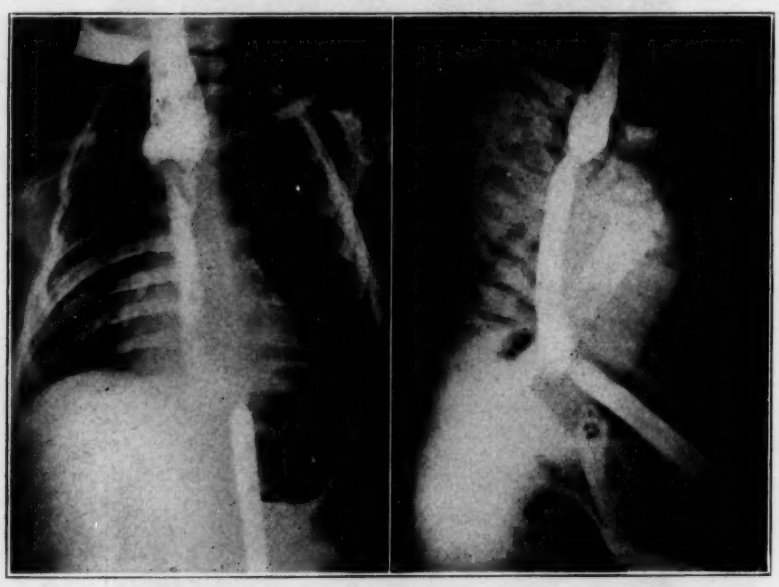

Fig. 3 (case 5).—Esophageal stricture at the point of anastomosis of a congenital esophageal atresia with tracheoesophageal fistula.

out at six month intervals for approximately four years. At present the child is swallowing normally and has remained free of symptoms. Roentgenograms have demonstrated that the lumen of the esophagus is adequate.

Case 5.—T. J., a female infant, was born in November 1946. It was recognized that she had a congenital atresia of the esophagus with a tracheoesophageal fistula. A surgical closure of the fistula with an anastomosis of the distal and proximal segments of the esophagus was successfully accomplished. The infant was discharged from the hospital and apparently swallowed satisfactorily until about 5 months of age. At this time difficulty in swallowing became more and more apparent, and consequently she was referred for esophageal dilation. Roentgenograms (fig. 3) demonstrated a prominent obstruction at the point of the previous anastomosis, and some food debris was removed from the stenosis. However, it was impossible to reestablish the lumen from above, and consequently a gastrostomy was performed. After the gastrostomy opening had healed, it was possible to reestablish the lumen by retrograde esophagoscopy, and subsequently the stricture in the esophagus was dilated by retrograde bougies passed over a

string. Dilations have progressed satisfactorily, but on several occasions the infant has been admitted to the hospital with food lodged in the stricture, and it has been necessary to remove the impacted food before she could swallow even her own saliva. She is now over 2 years of age and well nourished. Because of the tortuous esophagus at the region of the anastomosis, it has been necessary to leave the string in place for purposes of dilation. An incidental note in relation to this discussion is the fact that tracheal stenosis has been a complication in this infant, the stenosis occurring at the point of the esophageal-tracheal fistula.

CASE 6.—V. R., a girl 20 months of age, had been vomiting all food and fluids for two days. There was no history of a foreign body accident, but roentgenograms of the chest had demonstrated a double-pointed upholstery tack, points upward, located in the esophagus midway between the clavicles and the diaphragm (fig. 4). The round portion of the tack, 12 mm. in diameter, rested about 3 cm.

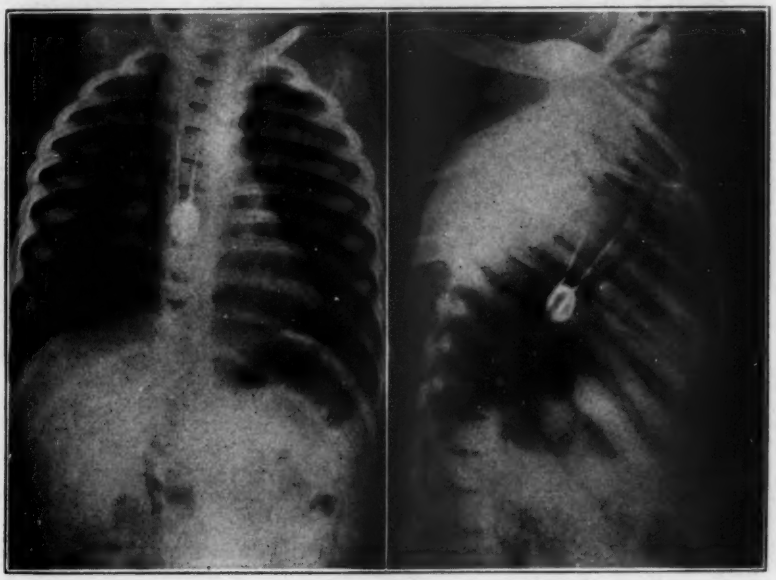

Fig. 4 (case 6).—Double-pointed upholstery tack located in the distal part of the esophagus of a 20 month old infant.

above the level of the diaphragm. The two sharp metallic prongs extended upward from the proximal limit of the round head of the tack approximately 3.5 cm. and the points were separated 12 mm. at their proximal tips. The position of the foreign body suggested the possibility that a stricture of the esophagus had prevented the forward motion of the foreign body. It was determined that the entire foreign body was metallic by testing it with a duplicate which could easily be held by a magnet. Consequently, an attempt was made to advance the foreign body into the stomach by means of the magnet with the idea that the object could then be rotated and removed with the points trailing. However, the original suspicion that the child had a congenitally short esophagus was confirmed because it was impossible to advance the foreign body downward; consequently, the two points were brought together with a safety pin closer, the esophagoscope advanced over the pointed parts of the tack and the tack withdrawn. Dysphagia continued after removal of the foreign body. Roentgenographic examination with

barium sulfate demonstrated almost complete stenosis of the esophagus at the point at which the foreign body had lodged (fig. 5), and, therefore, the esophagus was dilated esophagoscopically. The upper part of the esophagus was filled with a large quantity of food and fluid. The site of the stricture was found to be tight but smooth, and, although the esophagoscope passed through the stricture to improve the swallowing function, this did not return to normal. A second esophagoscopic examination was made, and a large olive pit was found impacted in the stricture. The pit had apparently been present in the esophagus for a long time in view of the fact that it was foul smelling and covered with exudate. Following this removal and another dilation, the child swallowed normally. Further discussion with the patient's family revealed the fact that the child had always

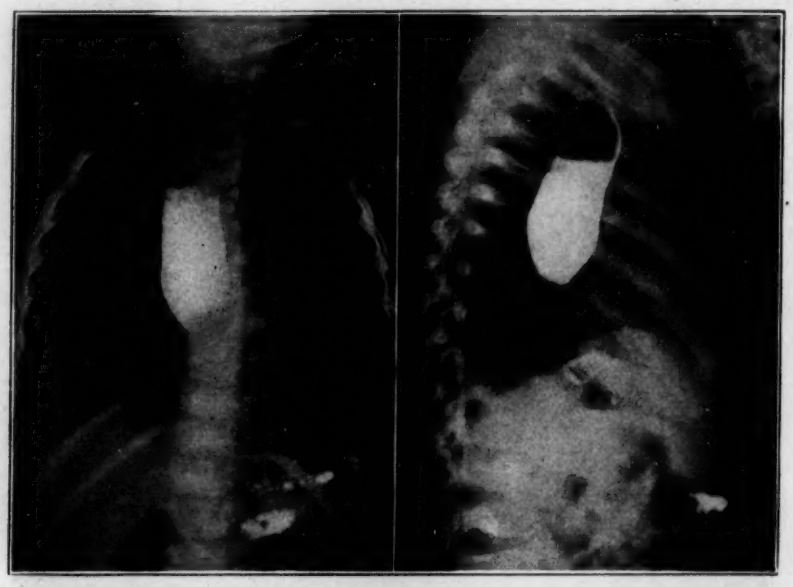

Fig. 5 (case 6).—Roentgenograms made after the ingestion of barium sulfate showing the pronounced esophageal dilatation above the stricture.

had difficulty in swallowing, taking liquids easily but having great difficulty with semisolid and solid foods. Since the dilation of the esophagus, this symptom has improved.

COMMENT

There are three types of congenital esophageal lesions which should be considered in this discussion: congenitally short esophagus, congenital esophageal stenosis and stricture of the esophagus which may follow the repair of a congenital esophageal atresia. The third type is self evident and may be disposed of briefly. It is illustrated by case 5. By the time the infant is old enough to swallow solid food or foreign bodies, the physician and family are well aware of the esophageal lesion and its problems and understand the signs and symptoms of obstruction. They return the child to the hospital for removal of the obstructing food particles, and dilations of the stricture

are carried out to permit the child to resume normal feeding. Rarely is there any question of diagnosis. However, it is important to stress that in any infant who has been successfully operated on for a congenital esophageal atresia with tracheal fistula the esophagus may become obstructed when semisolid and solid foods are added to the diet. Continued observation with occasional studies of the esophagus with the use of iodized oil or barium sulfate will be of benefit in detecting a gradual narrowing of the esophageal lumen at the point of anastomosis before obstruction becomes complete. Failure to recognize increasing obstruction may result in the obliteration of the lumen, making subsequent dilations exceedingly difficult and hazardous. Occasional early dilations will not be difficult and may save months of tedious effort to recanalize a completely obstructed lumen.

The other two principal types of congenital stenoses of the esophagus present distinctly different roentgenographic and esophagoscopic findings, although their symptomatology is identical. These anomalies, the congenitally short esophagus and the congenital esophageal stenosis, usually present no symptoms during the first five months of life. The infants are on a completely liquid diet and fluids pass through the stenotic areas without appreciable hesitation. When semisolid foods are added to the diet, feeding problems manifest themselves by slow eating and a reluctance to take anything but liquids. Often the family becomes accustomed to the length of time it takes to feed such an infant, but the child is sooner or later labeled a "feeding problem." When solids are added to the diet, frequent episodes of temporary obstruction occur with drooling, vomiting of undigested food and loss of weight. The child soon realizes he must refuse solid food entirely, thus further leading to the supposition that he is a "feeding problem." Bizarre eating habits develop, with the result that as the child grows older the time used to consume a meal may extend to an hour or more. Finally, episodes of complete obstruction occur which require esophagoscopic removal of a foreign body—a piece of meat, an orange seed, a toy or a coin.

Thus, the history of a congenital obstruction of the esophagus is quite characteristic of that of obstruction but gives no information in regard to the type of anomaly which is present. Differentiation between a congenitally short esophagus and a congenital esophageal stenosis is best made by roentgenographic and esophagoscopic examinations. The roentgenograms of a child with a congenital stenosis demonstrate a prominent dilatation of the upper portion of the esophagus, with a thin, irregular strand of barium sulfate of varying length from the point of the stenosis to the diaphragm and to the stomach itself (fig. 6). Such a stenosis may be 1 to 10 cm. in length, depending on the age of the child (cases 3 and 4); if the area of

stenosis is short it suggests the appearance of a cardiospasm (case 6). Esophagoscopically, such areas of stenosis are found abruptly terminating what appears to be a normal esophageal lumen. They lie in the middle of the thorax halfway to the diaphragm or below this point. The mucosa immediately around the stenosis is severely inflamed and often covered with granulation tissue, and the stricture responds readily to dilation, bougies passing into the stomach without appreciable resistance. After gradual dilation with bougies, an esophagoscope can be advanced through the upper point of the stricture into a granulomatous, inflamed lumen which does not have the normal esophageal

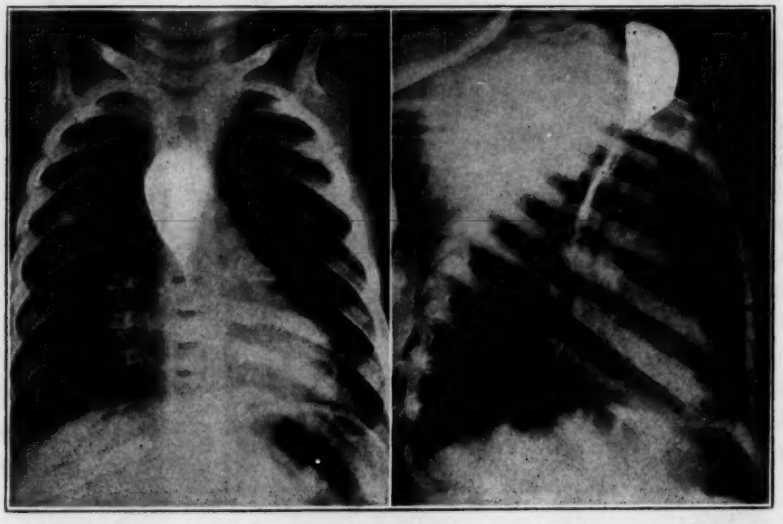

Fig. 6.—Congenital stenosis of the distal two thirds of the esophagus.

mucous membrane covering. This area remains inflamed until subsequent dilations eventually relieve the stenosis and the granulation tissue is replaced by a smooth, although considerably reddened mucosal surface. These strictures respond rather satisfactorily to dilation; following the first or second dilation the child is able to eat normally and his entire personality changes.

The second type of congenital stenosis, the so-called congenitally short esophagus, presents an entirely different picture both roentgenologically and esophagoscopically (cases 1 and 2). The following description of the roentgenologic finding by Clerf and Manges [1] is significant:

1. Clerf, L. H., and Manges, W. F.: Congenital Anomalies of the Esophagus, with Special Reference to the Congenitally Short Esophagus with a Portion of Stomach Above the Diaphragm, Ann. Otol., Rhin. & Laryng. **42**:1058 (Dec.) 1933.

The essential points in the roentgen ray diagnosis of congenital shortening of the esophagus are, first, a portion of the cardiac end of the stomach must be shown to stay above the level of the diaphragm; second, the esophagus must be shown to be too short to reach as low as the level of the diaphragm. As to the first point, the only characteristic sign is the presence of longitudinal rugae markings in that portion of the tube just above the diaphragm. When this point is established, then change of posture will not cause that portion of the stomach above the diaphragm to go either lower or higher, and there will be no variation in relations on repeated studies.

Cases of congenital shortening of the esophagus are almost invariably associated with a point of pronounced narrowing at the true cardia. It is at this point that the foreign body becomes lodged, and the condition is first recognized after the removal of the foreign body and confirmation by roentgenologic studies. The area of narrowing is generally at the level of the seventh or eighth dorsal vertebrae.

Esophagoscopically, the congenitally short esophagus has an entirely different appearance from that of the congenital esophageal stenosis. The mucosa at the cardia which now lies well above the level of the diaphragm is smooth and the stricture is firm. An esophagoscope can be passed through the stenosis only with great difficulty, and response to dilation is not nearly as satisfactory as the response to dilation of the congenital esophageal stenosis. If the esophagoscope can be passed through the stenotic area, gastric rugae are visualized immediately below the stenosis with the characteristic bright red, velvety appearance of gastric mucous membrane. Treatment again is repeated dilation by any of the methods commonly employed with the esophagus. The response to treatment, as mentioned, is not as satisfactory as for congenital stenosis.

As every pediatrician knows, foreign body accidents in children are common; when the object is ingested, not aspirated, the greatest percentage passes through the gastrointestinal tract without any difficulty whatsoever. In a review of our cases of foreign bodies that required endoscopic removal from the air and food passages, a series of 1,026 consecutive cases comprising 1,076 separate foreign bodies was reported.[2] Of these, 646, or 63 per cent, were in children under 14 years of age and 480, or 47 per cent, in children under 5 years of age. Of the total number of cases, the foreign body was found in the esophagus in 604, or 56 per cent, of cases. Division of this group of 604 esophageal foreign bodies showed that the anatomic location of 436, or 73 per cent, was in the cervical area of the esophagus, 118, or 19 per cent, in the thoracic part and 50, or 8 per cent, in the cardiac part. These

2. Holinger, P. H.; Andrews, A. H., Jr., and Anison, G. C.: Pulmonary Complications Due to Endobronchial Foreign Bodies, Illinois M. J. **93**:19 (Jan.) 1948.

statistics are of great importance in regard to the present discussion. It will be noted that approximately 75 per cent of esophageal foreign bodies lodge in the cervical part of the esophagus immediately below and behind the level of the larynx. This is the point to which the strong muscles of the hypopharynx carry the object and from which the weaker muscles of the esophagus cannot continue it on its travels. Since this location is so frequently the site of lodgment in the normal esophagus, further roentgenologic studies following the removal of the object are generally not necessary. If, on the other hand, a roentgenogram of the child who has swallowed a foreign body demonstrates the foreign body to be lodged in any position in the esophagus other than in the cervical part it becomes important to perform careful fluoroscopic and roentgenographic studies following the removal of the foreign body. It is important, too, to attempt to elicit the history of previous foreign body accidents and to determine whether the child has been a feeding problem. The fluoroscopic study should be a standard rule following any esophageal foreign body accident in which the foreign body lodges elsewhere than in the cervical portion of the esophagus.

SUMMARY AND CONCLUSIONS

Children of any age may swallow food or nonedible objects which will become lodged in the esophagus. The commonest site of lodgment of such objects is the cervical portion where the esophagus normally reaches its narrowest point. The strong muscles of the hypopharynx will carry the object to this point, but the weaker muscles of the esophagus fail to continue it on its course. If the esophagus is normal and the foreign body has passed this narrow point safely, it may be considered as a general rule that it should continue into the stomach without further arrest. Therefore, if an object lodges in a position other than in the cervical part of the esophagus, careful roentgenologic studies of the entire esophagus should be carried out to determine whether some anomaly, congenital or acquired, is responsible for the unusual position of the foreign body.

Congenital anomalies of three types may be responsible for the lodgment of foreign bodies in a position other than in the cervical part of the esophagus. These are congenital esophageal stenosis, congenitally short esophagus or congenital atresia of the esophagus with a tracheoesophageal fistula, the repair of which has been followed by the formation of a stricture at the point of the anastomosis.

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ACUTE ACETYLSALICYLIC ACID INTOXICATION

Report of Five Cases with Two Deaths

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TOXICITY due to acetylsalicylic acid U.S.P. is now receiving the increased attention of the pediatrician. In a period of one year, following the case report of one of us (S. O. K.) and Bernstein,[1] we have seen 4 additional cases of acetylsalicylic acid poisoning in the wards of the Jewish Hospital; 3 cases in the pediatric service alone, 1 of which resulted in death. This comprises a total of 5 cases, with 2 deaths, a mortality of 40 per cent.

In a review of the American literature, poisoning due to overdose of acetylsalicylic acid appears to occur so infrequently that there have been only 7 previously reported deaths.[2] In direct contrast to the rarity of acetylsalicylic acid poisoning in this country were the 752 cases and 4 deaths from 1924 to 1929 reported by Balázs [3] from Budapest, Hungary, and the numerous others in the British literature.[4]

From the pediatric and medical services of the Jewish Hospital.

1. Krasnoff, S. O., and Bernstein, M.: Acetylsalicylic Acid Poisoning, with a Report of a Fatal Case, J. A. M. A. **135**:712-714 (Nov. 15) 1947.

2. Krasnoff and Bernstein.[1] Ashworth, C. T., and McKemie, J. F.: Hemorrhagic Complications with Death Probably from Salicylate Therapy: Report of Two Cases, J. A. M. A. **126**:806-810 (Nov. 25) 1944. Hawkinson, O., and Kerr, E. K.: A Case of Granulocytopenia with Severe Anemia and Staphylococcemia Where the Only Etiological Factor Was the Use of Aspirin in 40-60 Grain Doses Daily for Years, Illinois, M. J. **83**:168-170 (March) 1943. Friedman, J. H.: Toxic Encephalopathy: Coal Tar Derivatives as a Probable Etiological Factor; Report of Three Cases with Neurohistological Studies in Two, J. Mt. Sinai Hosp. **5**:463-471 (Nov.-Dec.) 1938. Troll, M. M., and Menten, M. L.: Salicylate Poisoning: Report of Four Cases, Am. J. Dis. Child. **69**:37-43 (Jan.) 1945.

3. Balázs, J.: Ueber Azetylsalizylsäure (Aspirin)-Vergiftungen, Med. Klin. **26**:1664-1666 (Nov. 7) 1930.

4. Wyllie, A. M.: A Fatal Case of Aspirin Poisoning, with Post-Mortem Findings, Lancet **2**:768-769 (Oct. 5) 1935. Biddle, E.: Aspirin Poisoning, Brit. M. J. **1**:1365 (June 25) 1938. Neale, A. V.: Aspirin Poisoning, ibid. **1**:109-110 (Jan. 18) 1936. Hopkins, P.: Aspirin Poisoning: Report of a Case, Lancet **1**:145 (Feb. 3) 1945. Lewis, F. W.: A Case of Aspirin Poisoning, ibid. **1**:64 (Jan. 11) 1919. Dyke, S. C.: Aspirin Poisoning, ibid. **2**:613-614 (Sept. 14) 1935.

REPORT OF CASES

CASE 1.—(A set of twins [cases 1 and 2] was received simultaneously.) R. T. B., a white male infant, 5 months of age, weighing about 7,500 Gm., was admitted Sept. 10, 1947 with the complaint of "fever and diarrhea." On September 9, one day prior to hospitalization, the baby had a mild infection of the upper respiratory tract. The mother misinterpreted instructions given by her family physician in a telephone conversation, with the result that the baby was given acetylsalicylic acid, 0.32 Gm. (5 grains), with sodium bicarbonate, 4.0 Gm. (60 grains), every two hours for eight doses. This made a total dosage, all of which was retained, of 2.56 Gm. of acetylsalicylic acid and 32 Gm. of sodium bicarbonate in fourteen hours. Thereafter the baby had fever, with a temperature which reached 42.2 C. (108 F.) per rectum by 12:30 a. m., September 10. The infant was admitted to the hospital at 1:40 a. m.

Physical Examination.—The pertinent findings were as follows: The temperature was 42.2 C. per rectum, and the baby was comatose, with cyanosis of the skin and mucous membranes. The infant showed peripheral vascular failure with extreme tachycardia and imperceptible pulse. A sweet odor to the breath was noted.

Clinical Course and Treatment.—Immediate continuous intravenous infusion of 5 per cent dextrose solution in lactated Ringer's solution U. S. P. was started. However, the baby died three hours after admission to the hospital.

Report of Autopsy.—The following is an abridgment of the autopsy observations on this infant. Examination of the pleura showed petechial hemorrhages and small ecchymotic areas over the visceral pleurae. There was minimal fluid present. The pericardium showed petechial hemorrhages. The myocardial tissues were firm and pale, and the right atrium was somewhat dilated. The lungs were slightly atelectatic, and the cut surfaces showed solid red areas of hemorrhage alternating with normal parenchyma. Hemorrhagic areas were present in all lobes. One small petechial hemorrhage was present in the mucosa of the stomach. The liver weighed 200 Gm. The capsule was smooth, and the cut surface was pale yellow-brown. Microscopically, the myocardial tissues showed edema. The lungs were hemorrhagic and edematous and had areas of focal necrosis. The splenic tissues were congested and showed areas of slight hemorrhage. Adrenal hyperplasia was present. The kidneys had slight dilatation of Bowman's capsule with beginning vacuolization of the cells of the distal tubules. In the liver prominent hydropic degeneration was present. There was severe edema with prominent Desse's spaces and compression of the sinusoids.

Chemical Analysis.—The liver, kidneys, blood and urine contained salicylates in high concentration (coroner's report).

The cause of death was acute acetylsalicylic acid intoxication.

CASE 2.—D. B., a white male infant 5 months of age, weighing about 8,400 Gm., the twin of R. T. B. (case 1), was admitted at the same time with the same history as his twin, except that this child received 0.32 Gm. less of acetylsalicylic acid and 4 Gm. less of sodium bicarbonate than his sibling.

Physical Examination.—The pertinent findings were as follows: The temperature was 41.7 C. (107 F.) rectally, and the baby was comatose, with brief generalized clonic convulsions occurring at frequent intervals. There was cyanosis of the skin and mucous membranes. The pupils were in midcontraction and did not respond to light. The lips were dry, and the breath had a sweet odor. The heart rate was 160, with a weak and thready pulse. The respirations were hyperpneic.

Clinical Course and Treatment.—The baby was given phenobarbital sodium U.S.P., 0.32 Gm., subcutaneously, which controlled the convulsions, and an immediate intravenous infusion of 5 per cent dextrose solution in lactated Ringer's solution was begun. Nine hours after his admission, the temperature, which had meanwhile fallen to 37.9 C. (100.2 F.), rose to 40.0 C. (104 F.) and the patient again had convulsions. Lumbar puncture released a crystal clear fluid under greatly increased pressure (380 mm. of water). The convulsions then ceased, and the temperature abruptly fell to normal. Further improvement was rapid, and the baby was discharged in good condition on September 20.

CASE 3.—K. B., a white female infant 6 months of age, weighing about 7,000 Gm., was admitted to the hospital on Oct. 25, 1947 with the complaint of "rapid, deep breathing." On October 20, five days prior to her admission, the baby had a mild infection of the upper respiratory tract, and a prescription was given for a medicament containing acetylsalicylic acid, 0.18 Gm. (3 grains) to the dose, which was taken every four hours for five days (total, 5.4 Gm. or 90 grains). All the medicament was retained. The mother noticed abnormal respirations on October 22, three days prior to admission, and at the same time the infant became irritable and restless and slept poorly. Anorexia developed, but vomiting did not occur until October 25. Diarrhea was not present. The past history and family history were not pertinent. The developmental and dietary histories were normal.

Physical Examination.—The essential findings were as follows: The temperature was 39.1 C. (102.4 F.) rectally, and the respiratory rate varied from 60 to 100 per minute. The respirations were hyperpneic. The patient was extremely irritable but appeared fairly vigorous. No other abnormal findings were present.

Clinical Course and Treatment.—The patient had a sustained fever which reached peaks of 40.5 C. (104.9 F.) rectally. Pronounced irritability continued and all oral feedings were refused. On the third day in the hospital, severe generalized clonic convulsions developed and distention of the anterior fontanel was noted. The temperature was 40.5 C. A lumbar puncture was performed and crystal clear spinal fluid spurted out under an initial pressure of 420 mm. of water. This measure did not relieve the convulsions, although the fever promptly subsided. Phenobarbital sodium, 0.09 Gm. (1.5 grain), was given intravenously in divided doses and arrested the convulsions. The following day the baby had a recurrence of convulsions which reacted favorably to phenobarbital sodium, 0.03 Gm. (0.5 grain), and failed to respond to lumbar puncture, although fever and distention of the fontanel were again present.

Additional treatment comprised intravenous administration of 10 per cent dextrose solution in lactated Ringer's solution continuously for four days, vitamin K intramuscularly, oxygen therapy and several blood transfusions. The baby remained critically ill for six days and recovered without residua.

CASE 4 (previously reported[1]).—J. K., a 54 year old white man, was admitted to the hospital at 6:30 p. m., June 24, 1946. He had hypertension for many years. On the night prior to admission, he ingested 15 to 20 0.3 Gm. tablets of acetylsalicylic acid (5 to 6.1 Gm.) in a period of three hours. Early the next morning he was quite restless and incoherent and complained of tinnitus and deafness in the left ear. He was anuric and became progressively stuporous; when he was admitted to the hospital, his temperature was 41.0 C. (105.8 F.), the pulse rate 154, the respiratory rate 32 and the blood pressure 170 systolic and 90 diastolic. His face was flushed; the pupils were small and did not react to

light, and the eyes were rotated upward and outward. There were moist rales throughout both pulmonary fields. Pinpoint petechiae were seen over the abdomen. There was a generalized hyporeflexia. Despite many therapeutic measures, including artificial antipyresis and rapidly acting stimulants, the patient died at 11:15 p. m. on the night of his admission.

Autopsy Reports.—An autopsy performed ten hours after death by Dr. Helen Ingleby, of the department of pathology, revealed many subpericardial, as well as subpleural, hemorrhages. The heart presented a parboiled appearance, and all its chambers were well dilatated. The lungs were intensely congested, as were the pancreas and spleen. The surfaces of the kidney were studded with petechiae, and the cut surfaces presented evidence of cloudy swelling. The stomach contained bile-stained material and revealed many petechiae and a few submucosal hemorrhages. The liver was congested and mottled with yellow fatty patches. The brain also was intensely congested.

Microscopic examination of the heart revealed fragmentation and swelling of the smooth muscle fibers and a few pericardial hemorrhages. The lungs showed intense alveolar hemorrhage, and the liver confirmed the gross evidence of congestion and showed many large and small vacuoles, as well as hydropic degeneration with beginning necrosis. Sections of the kidney showed glomeruli intensely congested with blood and debris, almost complete degeneration of the proximal convoluted tubules and separation from their basement membrane of the cells of the distal convoluted tubules. The brain revealed cerebral atherosclerosis, cortical and subcortical degeneration, areas of necrosis (pallidum and temporal lobe) and fatty degeneration of the cells of the medulla.

A postmortem specimen of blood and the contents of the stomach were qualitatively strongly positive for acetylsalicylic acid.

The cause of death was acute acetylsalicylic acid intoxication.

Case 5.—G. S., a 21 year old white woman, was admitted to the hospital at 8:15 a. m., April 12, 1947. She had ingested approximately 100 0.3 Gm. tablets of acetylsalicylic acid (33.3 Gm.) about 1 a. m. the same morning. At 7 a. m. a strong emetic had been administered at home. The vomitus contained a great deal of "white powdery material." On her admission the patient complained of nausea, tinnitus, deafness and paresthesias in the hands and feet. She was moderately restless. The temperature was 37.2 C. (99 F.), the pulse rate 129 and the respiratory rate 28. The blood pressure was 105 systolic and 70 diastolic. Her pupils were contracted and did not react to light. The urine showed the presence of albumin, acetone and diacetic acid. The blood carbon dioxide-combining power was 40 volumes per cent and the prothrombin time was 20 seconds (normal, 15 seconds). All other laboratory findings were normal.

The patient was given 2,000 cc. of sixth-molar sodium lactate solution intravenously, 60 mg. of menadione sodium bisulfite U.S.P. (hykinone®) subcutaneously and general supportive therapy. On the third day in the hospital, the urine and the carbon dioxide-combining power were normal; the patient was asymptomatic. She was discharged fully recovered April 16.

COMMENT

It is evident from the pathologic observations in our cases, as well as in the fatal cases with necropsy reported by others, that most of the symptoms and signs of acetylsalicylic acid poisoning are the result of damage to the brain, kidneys and liver and concomitant changes in the electrolyte balance. The alterations in the electrolyte balance caused

by the salicyl radical produce many of the manifestations of poisoning from this substance, and a working knowledge of these changes is needed if prompt and proper treatment is to be instituted.

As stated by Erganian and his co-authors,[5] initially there is an uncompensated alkalosis due to hyperventilation produced by the stimulatory effect of the salicyl radical on the respiratory center. Compensation is rapidly brought about by the excretion of excess bicarbonate in the urine. At this stage the urinary p_H is alkaline. Guest and his co-workers [6] experimentally were able to return the p_H and the carbon dioxide tension to normal values by abolition of the hyperpnea through the use of pentobarbital sodium, which depressed the sensitivity of the respiratory center. Acidosis later develops, which is partially due to dietary and metabolic ketosis and is made even severer by the previous depletion of serum sodium bicarbonate. Dysfunction of the respiratory center, in addition to muscular fatigue, eventually causes cessation of the hyperventilation which is now necessary to rid the tissues of excess carbonic acid ions, and a state of uncompensated acidosis results.

The changes in acid-base balance occurring as a result of acetylsalicylic acid intoxication are summarized as follows:

1. Early Effects: Hyperpnea due to the central stimulatory effect of the salicyl radical produces a respiratory loss of carbon dioxide, altering the ratio of bicarbonate to sodium bicarbonate in the direction of increased alkalinity. This then is a state of respiratory alkalosis and represents the first stage of salicylate intoxication.

2. Later Effects: The next stage is a state of compensated acidosis caused by the ketosis resulting from altered carbohydrate metabolism and the presence of retained acid anions in the blood and tissue fluids. The alkali reserve has been lowered prior to this stage by excess elimination of sodium bicarbonate in an effort to compensate the stage of respiratory alkalosis. Compensation is now maintained by the renal and blood buffer systems and by the respiratory mechanism. The hyperpnea, which is now present, is due to the central effect of increased acidity of blood and tissue fluids.

3. Late Effects: The final stage is that of decompensated acidosis, with depletion of the alkali reserve, decrease in blood p_H and failure of the respiratory center in its attempt to achieve compensation.

With the increased general use of acetylsalicylic acid and other salicylates for nonspecific symptomatic treatment, one should be alert for early toxic manifestations. It has been our experience that for

5. Erganian, J. A.; Forbes, G. B., and Case, D. M.: Salicylate Intoxication in the Infant and Young Child, J. Pediat. **20**:129-145 (Feb.) 1942.

6. Guest, G. M.; Rapoport, S., and Roscoe, C.: The Effect of Salicylates on the Electrolyte Structure of Blood Plasma, J. Clin. Investigation **24**:770-774 (Sept.) 1945.

adequate antipyresis or analgesia 0.09 Gm. of acetylsalicylic acid per kilogram of body weight need not and should not be exceeded as the daily dose for infants and young children. Unusual symptoms and signs referable to the central nervous and renal systems, the gastrointestinal tract and the liver (as hepatotoxic effects leading to prothrombinopenia and evidenced by hemorrhage and petechiae) should make one suspect the possibility of intoxication by acetylsalicylic acid or other salicylates. Obviously, the early recognition of these symptoms and signs not only may prevent serious complications but may even be life saving.

TREATMENT

The treatment depends on the stage of salicylate intoxication.

In those cases seen early, cessation of use of the drug and gastric lavage with tap water are necessary. Lavage, however, is useless if hyperpnea has supervened. Sodium bicarbonate should not be used for gastric lavage, since it may increase the absorption of acetylsalicylic acid.[7] It is essential to give 5 or 10 per cent dextrose solutions intravenously in sufficient amounts to maintain fluid balance and provide carbohydrate. In the early stages it would seem wise to forego the use of alkaline solutions because of the alkalosis which is already imminent or existent.

In cases presenting the later stages of acidosis and ketosis, alkalinizing solutions of sixth-molar sodium lactate or 5 per cent sodium bicarbonate in sufficient amounts to correct the deficit of base should be administered. In milder stages of acidosis, sodium r-lactate in 5 or 10 per cent dextrose solution may be used.

Because of the severity and fixed nature of the acidosis, one should guard against early discontinuance of parenteral therapy, as there is a definite tendency for relapse to occur. Vitamin K and vitamin C should be given in all cases. Oxygen is extremely useful, and blood and plasma transfusions may be essential. In those cases reported by Zimmerman and Shapiro, the development of hypoprothrombinemia was prevented by supplemental vitamin K and the use of ascorbic acid was also advocated to lessen vascular vulnerability. Lumbar puncture is of aid in relieving hyperpyrexia and convulsions.

Useful laboratory procedure to guide therapy is determination of blood and urinary p_H and total base, as well as blood carbon dioxide–

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7. Barnett, H. L.; Powers, J. R.; Benward, J. H., and Hartman, A. F.: Salicylate Intoxication in Infants and Children, J. Pediat. **21**:214-223 (Aug.) 1942.

8. Zimmerman, S. P., and Shapiro, S.: Correlation Between Salicylate Dosage and Plasma Level and the Prothrombin Content of the Blood, Exper. Med. & Surg. **4**:110-117 (May) 1946.

combining power and blood chlorides. Prothrombin times should also be taken to estimate the degree of hypoprothrombinemia.

SUMMARY

1. The use of acetylsalicylic acid, sodium salicylate and other salicylate compounds has become widespread throughout the world. However, the acetylsalicylic acid tablet per se has been rarely thought of as a toxic agent.

2. A review of the toxic effects of the drug is presented, the clinical and pathologic pictures being rather characteristic.

3. The drug exerts its toxic effects primarily on the brain, liver and kidneys, but significant concentrations can be detected in all the tissues.

4. The profound alterations of acid-base balance, which are described, occur.

5. Five cases of toxicity due to acetylsalicylic acid are reported, with 2 deaths and autopsy observations in both.

6. Current concepts in the treatment of salicylate intoxication are discussed.

Dr. Mitchell A. Bernstein and Dr. Nathan Blumberg gave permission to include reports on the patients admitted to their services.

York and Tabor Roads.

SIX EXAMPLES OF PRECOCIOUS SEXUAL DEVELOPMENT

I. Studies in Diagnosis and Pathogenesis

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A GENERAL discussion of the problems involved in precocious sexual development of children was presented by one of us (H. P. G. S.) in 1946.[1] This publication and another one to follow are intended to amplify that general discussion with a presentation of 6 specific examples. The first of these publications deals with diagnostic and pathogenetic studies, while the second will be devoted to the aspects of growth and maturation in the same patients.[2] From the beginning, it seems to be of paramount importance to recognize the borderline between pathologic "precocity" of sexual development and what may be termed physiologic "early" sexual development. A few observations on the latter group of children may be briefly recorded with a view to avoiding diagnostic pitfalls and the consequences of calling children abnormal who are exuberantly healthy.

I. "EARLY" SEXUAL DEVELOPMENT

In normal boys "early" sexual development is rarer than in normal girls and makes its appearance about two years later. First signs of testicular growth and secondary sexual characteristics are sometimes observed between 9 and 11 years of age and near maturation at 12 to 13 years of age (two recent observations). Among large numbers of healthy girls, on the other hand, there will always be a few who show secondary sexual characteristics between the ages of 7 and 8 years and begin to menstruate between 8 + and 10 years. Six instances to substantiate this assertion were seen at the Bobs Roberts Hospital in recent years. In 2, only histories to that effect were obtained, while

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1. Seckel, H. P. G.: Precocious Sexual Development in Children, M. Clin. North America **30**:183 (Jan.) 1946.

2. Seckel, H. P. G.: Am. J. Dis. Child., to be published.

the other 4 were observed closely. These 4 girls showed figures for height and weight and degrees of sexual maturation normally seen in girls 12 to 15 years of age; their skeletal age was usually one to three years ahead of their chronologic age. For 1 of these girls, whose record follows, studies were made of urinary hormone.

CASE A.—Ruth C., a white girl born Feb. 10, 1937, was seen for the first time in the hospital at the age of 7 10/12 year with the chief complaint of premature sexual maturation. The history indicated that her breasts began to develop and

Fig. 1 (case A).—Girl, 7 10/12 years of age, with "early" sexual development Menarche occurred five months later. No abnormalities were present.

pubic hair to appear at 7 1/12 years. On her admission her nipples and breasts were well developed and pubic hair was present (fig. 1). No axillary hair or facial acne was noticed, however. She had slight hairiness of her legs. A biopsy specimen showed a nonsecretory endometrium. Her skeletal age was approximately 9 years and her dental eruption age, 8 years. Results of all clinical, roentgenologic and metabolic studies aimed at the potential causes of sexual precocity were within normal range. At 8 3/12 years of age menarche occurred, and menstruations were regular for the next three months of observation. Her mother's menstruations had started at 11 years. Between 7 10/12 years and 8 1/2 years of age, the patient's

weight had increased from 41.7 to 44.8 Kg. and her height from 137.5 to 144 cm. Urinary hormone studies[3] revealed a daily output of 4.8 mg. of 17-ketosteroids, less than 10 international units of estrogens, no pregnandiol and 0.4 mg. of cortin-like substance; all figures corresponded to her chronologic age.

While it is not proposed to search the literature for the point in question, reference may be made to an illustration in Brennemann's system.[4] A picture was given of a 9 4/12 year old girl with "physiological early puberty" who "commenced to show breast development at 7½ years of age. Menstrual periods started at 8 years." Her weight was 80 pounds (36.3 Kg.) and her height, 54½ inches (138.4 cm.); her maximum skeletal age was 13 years. The lower age limit for the first appearance of secondary sexual characteristics was cited by Stuart[5] as 7 3/12 years in girls and 10 9/12 years in boys (tenth year, Schonfeld[6]). Figures for urinary 17-ketosteroids in our patient are in good agreement with those reported in similar "early" cases by Nathanson and Aub[7] (cases 2, 6, 7 and 8) and by Hain[8] (3 cases). All writers stress the fact that children in the United States are about two years ahead in sexual development of those of other areas, including Europe. In all borderline cases of "early" development, repeated clinical, roentgenologic and, if possible, hormonal examinations are indicated, for the pathologic causes of sexual precocity may operate after 7 years, as well as prior to this age.

II. PRECOCIOUS SEXUAL DEVELOPMENT: REPORT OF CASES AND COMMENT

CASE 1.—Rosalie B. was a white girl born Feb. 26, 1940. The patient's parents, in 1947, were in their late twenties, of good health and living separately. The mother and her twin sister had had their menarche between 11 and 12 years; the mother measured 5 feet 2 inches (157.5 cm.) and weighed 112 pounds (50.8 Kg.). There was a younger brother, also in good health and of normal development (110 cm. and 20.9 Kg. at 5 years). No family history of sexual precocity was obtained. At full term on normal delivery the patient weighed 2,250 Gm. She cut her first tooth at 5 months, walked alone at 9 months and talked at 18 months.

3. Dr. R. I. Dorfman, Western Reserve University School of Medicine, Cleveland, made these studies. He cited normal values of 0.2 to 0.6 mg. per day for cortin in the adult female; for other normal values, see table 3.

4. Talbot, F. B., and Talbot, N. B.: Pituitary and Suprarenal Glands, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 1, chap. 40, fig. 10.

5. Stuart, H. C.: Normal Growth and Development During Adolescence, New England J. Med. **234**:666, 693 and 732, 1946.

6. Schonfeld, W. A.: Management of Male Pubescence, J. A. M. A. **121**:177 (Jan. 16) 1943.

7. Nathanson, I. T., and Aub, J. C.: Excretion of Sex Hormones in Abnormalities of Puberty, J. Clin. Endocrinol. **3**:321, 1943.

8. Hain, A. M.: The Constitutional Type of Precocious Puberty, J. Clin. Endocrinol. **7**:171, 1947.

At 7 years of age she attended parochial school in the second grade. She had chickenpox at 3 years without complicating encephalitis. Her abnormal sexual development started when she was 2½ years old, at which time enlargement of the breasts was first noticed. Shortly after her third birthday, she began to menstruate, at first discharging only a few drops of blood, but gradually regular mild flows of three days' duration developed. Ever since her menarche the cycles had occurred regularly about every twenty-eight days without discomfort. From 2½ to 5 years of age her breasts continued to grow and she surpassed her playmates in body growth. She never asked any questions regarding sex nor did she

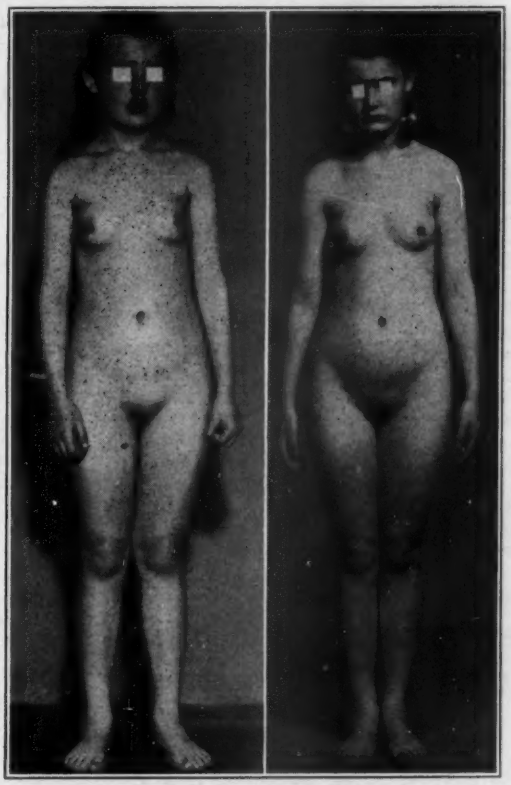

Fig. 2 (case 1).—Girl at 5 3/12 years of age (left) with isosexual precocity associated with congenital hyperplastic abnormality of the tuber cinereum. Note sparseness of pubic hair and infantile facial expression. The right view shows the same girl at 7 3/12 years of age, thirteen days before her death. Adolescent body, sparse pubes and infantile facial proportions are apparent.

show any interest in boys corresponding to her in developmental age. She preferred to play with children 8 to 9 years of age.

Physical Examination.—The patient was observed several times between the ages of 5 3/12 years (May 1945) and 7 3/12 years (May 1947). On each occasion she appeared excessively tall for her age and precociously matured (fig. 2). At 5 years of age she measured 137 cm. and weighed 35.3 Kg. and at 7 years, 147 cm. and 44.7 Kg. At 7 years her hips had the dimensions of those of a 16 year old adolescent girl. The glandular tissue of both breasts was well developed, and the

nipples were large and prominent but little pigmented. There was a remarkable contrast between this state of sexual development and the initial absence and later scarcity of pubic and axillary hair, which were first observed at the age of 6 9/12 years. The skin was of normal texture, no hypertrichosis, no acne and no facial seborrhea being in evidence. The face appeared infantile in contour and expression, and there were 12 deciduous and 10 permanent teeth in her mouth, as is normal for 7½ year old girls.

On gynecologic examination at and prior to the age of 6 9/12 years, the external genitalia showed some evidence of precocious development, the vagina admitting one

TABLE 1.—*Survey of Biochemical Data: All Cases*

Case no.	1			2	3	4	5	6	
Age, yr.	5¼	6¾	7¼	8¾	ca. 3	3¼	7⅛	4 1/12	9⅛
Basal metabolic rate									
Calories/sq. M.	38.5	43.2	34.4	49.0	....	....	....	....	45.5
% normal, chronologic age	−27	−13	−29	−4	....	....	....	....	−7
% normal, biologic age	−11	+14	±0	+6	....	....	....	....	+5
Blood dextrose, fasting,									
mg./100 cc.	....	80	98	95	....	....	71	69	100
Nonprotein nitrogen, mg./100 cc.	18	....	....	....	....	....	....	27	38
Urea nitrogen, mg./100 cc.	....	....	....	8.0	....	....	....	....	....
Creatinine, mg./100 cc.	0.79	1.0	0.8	....	....	....	....	....	....
Creatine, mg./100 cc.	2.74	3.3	....	....	....	....	....	....	....
Uric acid, mg./100 cc.	....	....	....	....	....	....	....	....	9.5; 7.9
Serum calcium, mg./100 cc.	9.9	10.6	10.4	10.9	....	9.4	11.0	11.3	10.0
Phosphorus, mg./100 cc.	4.4	4.8	4.1	4.6	....	5.3	5.5	6.45	4.08
Alkaline phosphatase,									
units/100 cc.*	9.9	10.6	10.4	7.2	....	5.4	6.8	....	9.5
Chlorides, mM/L.	105	....	103	98	....	....	†	....	101
Sodium, mEq./L.	....	....	....	134	....	....	....	....	....
Potassium, mEq./L.	....	....	....	4.7	....	....	....	....	....
Cholesterol, mg./100 cc.	135	188	137	....	....	125	....	130	110
Plasma albumin, Gm./100 cc.	....	....	....	....	....	....	....	....	4.69
Plasma globulin, Gm./100 cc.	....	....	....	....	....	....	....	....	2.49
Hemoglobin concentration,									
Gm./100 cc.	12.6	12.5	13.5	16.0	13.3	15.2	14.5	11.8	13.8
Red blood cells, millions/cu. mm.	4.55	4.8	5.30	5.23	4.70	5.53	4.31	....	5.09
Urinary creatinine, Gm./day	....	....	0.333	1.10	....	....	....	....	....
Urinary creatine, Gm./day	....	....	....	0.2	....	....	....	....	....

* Normal for children: 5 to 15 King-Armstrong units per hundred cubic centimeters (average 7.3 units).

† Blood chlorides measured 450 mg. per hundred cubic centimeters.

finger easily. There was no enlargement of the clitoris. The corpus of the uterus was estimated to be one-half to full adult size. The adnexa were not palpable and no abdominal pelvic masses were felt. An adnexal tumor could not be ruled out, however. An endometrial biopsy specimen taken at 5 3/12 years of age, on the second day of menstruation, showed "probable hyperplasia of the endometrium." At the age of 7 3/12 years the external genitalia appeared unusually mature, the hymenal ring was intact, the vagina admitted one finger and its mucosa was of adult type. The cervical surface appeared normal to palpation and inspection. The uterus was estimated to be of normal adult size and seemed to be pushed to the left and posteriorly. No palpable masses were found in either adnexa but the possibility of a right ovarian tumor was maintained. There were no neurologic signs, particularly none of a localizing hypothalamic nature, all the cranial nerves being normal in

action. The skin was free from pigmented spots. There were no palpable abdominal masses. Repeated blood pressure readings were around 110 mm. of mercury systolic and 80 diastolic.

Laboratory Data.—Intravenous pyelograms were normal on three admissions, and so was the roentgenographic appearance of the chest and skull, including the sella. Results of routine examinations of urine were normal. The Kahn reaction of

TABLE 2.—*Urinary Hormone Excretions per Twenty-Four Hours in Six Cases of Sexual Precocity**

Case no.	1		2		3		4		5	6	
Sex	Female		Male		Male		Male		Female	Female	
Age, yr	6¾	7¼	7½	8 11/12	2 7/12	3¼	3⅛	5 1/12	7⅛	9⅛	9¼
17-ketosteroids, total, mg	3.9†	4.6 6.5‡	6.4 11.5	8 to 9	2.0	2.0	5.0	45.2	36.3	25 to 53	20 to 38
Alpha-alcoholic, %	...	...	...	...	...	...	...	95	...	80 to 90	90
Beta-alcoholic, %	...	...	...	...	...	...	...	5	...	10 to 20	10
Androsterone, mg	...	...	...	...	...	...	...	13	...	18	...
Estrogens, I. U	8	17, 21	...	...	...	...	...	...	...	...	...
Pregnandiol, mg	...	0	...	...	...	...	...	...	...	...	...
Comment	...	...	...	...	...	...	...	...	...	Pre-operative	Post-operative

* Dr. R. I. Dorfman made determinations in cases 1 and 4 in his laboratory and Dr. A. T. Kenyon made those for cases 2, 3 and 5 in his; data on case 6 were obtained in the laboratory of one of us (W. W. S.).

† Specimen collected one day before menstruation.

‡ Five day specimen collected up to two days before menstruation.

TABLE 3.—*Normal Average Urinary Hormone Excretions per Twenty-Four Hours**

Age, years	2 to 5	6 to 10	11 to 16	11 to 18	Adult	Adult
Sex	Both sexes	Both sexes	Female	Male	Female	Male
17-ketosteroids, mg.	0.15 to 2	1.5 to 6	2.6 to 6.3	2.6 to 8.1	5 to 15 (9)	8 to 20 (14)
Androsterone, mg.	.....	0.1 to 0.3	0.3 to 0.7	0.5 to 3.0	0.5 to 1	1 to 11 (5.5)
Estrogens, I. U.	ca. 10	10 to 25	90 to 400	25 to 65	Up to 600	Up to 100
Pregnandiol, mg.	0 to trace	0 to trace	0 to plus	0	3 to 50	0

* This survey was taken from the table of one of us (H. P. G. S.)[1] and complemented by data from Hain,[5] Wooster (*J. Clin. Endocrinol.* **2**: 568, 1942) and Greulich and others (Somatic and Endocrine Studies of Puberal and Adolescent Boys, Monograph of the Society for Research in Child Development, 1942, vol. 7, no. 3).

the blood and the reaction to the intracutaneous tuberculin test (0.1 mg. of old tuberculin) were negative. Red and white blood cell counts and sedimentation rates were noncontributory. Oral dextrose tolerance tests gave normal results. For other biochemical and hormone data, see tables 1, 2 and 3. Roentgenologic studies of the bones revealed a maximum skeletal age of 14 to 17 years in the various portions of the skeleton, the most spectacular findings being the presence at 7 years of age of epiphysial centers in the acromion, coracoid process and iliac crest and of almost complete fusion of epiphysial lines at either end of the radius and ulna. At about 7 years of age her dental age by roentgenogram was

estimated to be 8 + years. Her sinus development corresponded to her chronologic age, as no frontal sinuses were in evidence. In psychometric tests she had intelligence quotients of 90 to 95 and a mental age a few months below her chronologic age. Her behavior was entirely on the level of a 5 to 7 year old girl and there was no psychosexual maturation.

Course.—In May 1947, with the diagnostic evidence available, it was the consensus that an exploratory pelvic laparotomy was indicated. This was performed with the patient under anesthesia induced by cyclopropane and ether on May 28, 1947. Inspection of the peritoneal cavity revealed a uterus normal in size for a virginal adult, well developed tubes and ovaries containing several mature follicles. Wedge specimens were taken for biopsy from both ovaries and the appendix was removed. Palpation of the suprarenal areas failed to reveal any abnormal masses. Following extraction of two deciduous teeth, done at the end of an uneventful period of general anesthesia, the patient suddenly stopped breathing. In spite of all efforts to revive her by means of artificial respiration and cardiovascular stimulants, she died about one and one-half hour after the abdomen had been closed.

Postmortem Examination.—In accordance with the general development of the girl, the weights of such organs as the heart, lungs, liver, pancreas, kidneys and brain were closer to adult standards than to standards for a normal 7 year old child. With the exception of the brain, these organs were anatomically normal on gross and microscopic examination.

At the base of the brain there was a white, nodular, egg-shaped, pedunculated mass lying beneath the right mamillary body and enclosed by meningeal tissue (fig. 3). The mass measured 0.9 by 0.6 cm. There were slight but definite pressure grooves in the surfaces of the hypocampal gyri, more extensive on the right than on the left. Similar flattening grooves were in evidence over the right clinoid process and the posterior surface of the sphenoid bone. The mass was attached posteriorly by a thick stalk to the right anterior superior aspect of the pons and anteriorly by two fine white filaments to the posterior portion of the hypothalamus just in front of the right mamillary body. Microscopically, the mass consisted of normal-appearing, non-neoplastic nerve tissue resembling that of the tuber cinereum. The anterior peduncle consisted of nerve fibers, the posterior one of meningeal fibrous tissue. The hypophysis weighed 540 mg. On the Mallory stain, the gland was largely composed of eosinophilic cells with relatively few dark-staining basophils present; there were many pale cells with fine basophilic stippling.

The nongonadal internal genital organs were those normally observed in an adult nulliparous woman. This was particularly true of the uterine proportions and measurements. The size and weight of the ovaries could not be reliably determined because wedge specimens had been taken for biopsy bilaterally; a rough estimate of the weight of one ovary was 5 Gm. (a normal adult ovary weighs 5 to 10 Gm.) and of the size, 2.5 by 1.5 cm. On microscopic examination many primordial follicles were present in the ovaries, besides one developing follicle and several small follicular cysts; there were no corpora lutea. The fallopian tubes showed a normal postmenarcheal appearance. The endometrium was that of a normal early premenstrual phase with well developed glands and decidua. The vaginal epithelium was normal for a virginal adult. The mammary glands were largely composed of ducts with small acini and appeared normal for a nonpregnant, ovulating female. The thyroid, parathyroids, adrenal medulla and pancreatic islands were all normal (the weight of the thyroid was 10 Gm.). The adrenals

weighed 3.5 Gm. each, the cortex measuring 1 mm. in average breadth. Microscopically, the glomerulosa was compact, with a high concentration of small cells with vesicular nuclei. Although few mitoses were in evidence, this zone had the appearance of actively proliferating tissue. The fasciculata was moderately rich in lipid.

The epiphysial lines at the distal end of the femur and the medial ends of the clavicles were almost closed. Microscopically, the cartilaginous portion of the

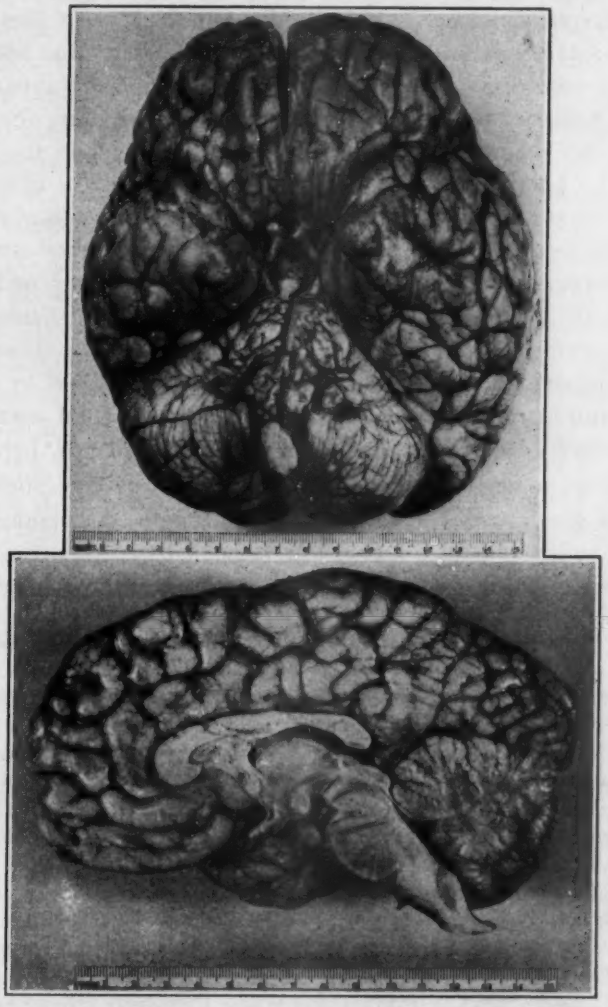

Fig. 3 (case 1).—The upper part shows base of brain of same girl as in figure 2. Note pea-sized pedunculated mass underneath the right mamillary body. The mass consisted of normal tuber cinereum cells. The lower part is the median sagittal section through the brain. Note pea-sized mass attached posteriorly to the pons and anteriorly to the tuber cinereum adjacent to the right mamillary body.

distal femoral epiphysis was thin and moderately active. Bone formation was evident on the metaphysial side of the cartilage but had almost ceased on the epiphysial side. The microscopic appearance of the clavicular epiphysis was similar to, but less active than, that of the femoral epiphysis.

estimated to be 8 + years. Her sinus development corresponded to her chronologic age, as no frontal sinuses were in evidence. In psychometric tests she had intelligence quotients of 90 to 95 and a mental age a few months below her chronologic age. Her behavior was entirely on the level of a 5 to 7 year old girl and there was no psychosexual maturation.

Course.—In May 1947, with the diagnostic evidence available, it was the consensus that an exploratory pelvic laparotomy was indicated. This was performed with the patient under anesthesia induced by cyclopropane and ether on May 28, 1947. Inspection of the peritoneal cavity revealed a uterus normal in size for a virginal adult, well developed tubes and ovaries containing several mature follicles. Wedge specimens were taken for biopsy from both ovaries and the appendix was removed. Palpation of the suprarenal areas failed to reveal any abnormal masses. Following extraction of two deciduous teeth, done at the end of an uneventful period of general anesthesia, the patient suddenly stopped breathing. In spite of all efforts to revive her by means of artificial respiration and cardiovascular stimulants, she died about one and one-half hour after the abdomen had been closed.

Postmortem Examination.—In accordance with the general development of the girl, the weights of such organs as the heart, lungs, liver, pancreas, kidneys and brain were closer to adult standards than to standards for a normal 7 year old child. With the exception of the brain, these organs were anatomically normal on gross and microscopic examination.

At the base of the brain there was a white, nodular, egg-shaped, pedunculated mass lying beneath the right mamillary body and enclosed by meningeal tissue (fig. 3). The mass measured 0.9 by 0.6 cm. There were slight but definite pressure grooves in the surfaces of the hypocampal gyri, more extensive on the right than on the left. Similar flattening grooves were in evidence over the right clinoid process and the posterior surface of the sphenoid bone. The mass was attached posteriorly by a thick stalk to the right anterior superior aspect of the pons and anteriorly by two fine white filaments to the posterior portion of the hypothalamus just in front of the right mamillary body. Microscopically, the mass consisted of normal-appearing, non-neoplastic nerve tissue resembling that of the tuber cinereum. The anterior peduncle consisted of nerve fibers, the posterior one of meningeal fibrous tissue. The hypophysis weighed 540 mg. On the Mallory stain, the gland was largely composed of eosinophilic cells with relatively few dark-staining basophils present; there were many pale cells with fine basophilic stippling.

The nongonadal internal genital organs were those normally observed in an adult nulliparous woman. This was particularly true of the uterine proportions and measurements. The size and weight of the ovaries could not be reliably determined because wedge specimens had been taken for biopsy bilaterally; a rough estimate of the weight of one ovary was 5 Gm. (a normal adult ovary weighs 5 to 10 Gm.) and of the size, 2.5 by 1.5 cm. On microscopic examination many primordial follicles were present in the ovaries, besides one developing follicle and several small follicular cysts; there were no corpora lutea. The fallopian tubes showed a normal postmenarcheal appearance. The endometrium was that of a normal early premenstrual phase with well developed glands and decidua. The vaginal epithelium was normal for a virginal adult. The mammary glands were largely composed of ducts with small acini and appeared normal for a nonpregnant, ovulating female. The thyroid, parathyroids, adrenal medulla and pancreatic islands were all normal (the weight of the thyroid was 10 Gm.). The adrenals

weighed 3.5 Gm. each, the cortex measuring 1 mm. in average breadth. Microscopically, the glomerulosa was compact, with a high concentration of small cells with vesicular nuclei. Although few mitoses were in evidence, this zone had the appearance of actively proliferating tissue. The fasciculata was moderately rich in lipid.

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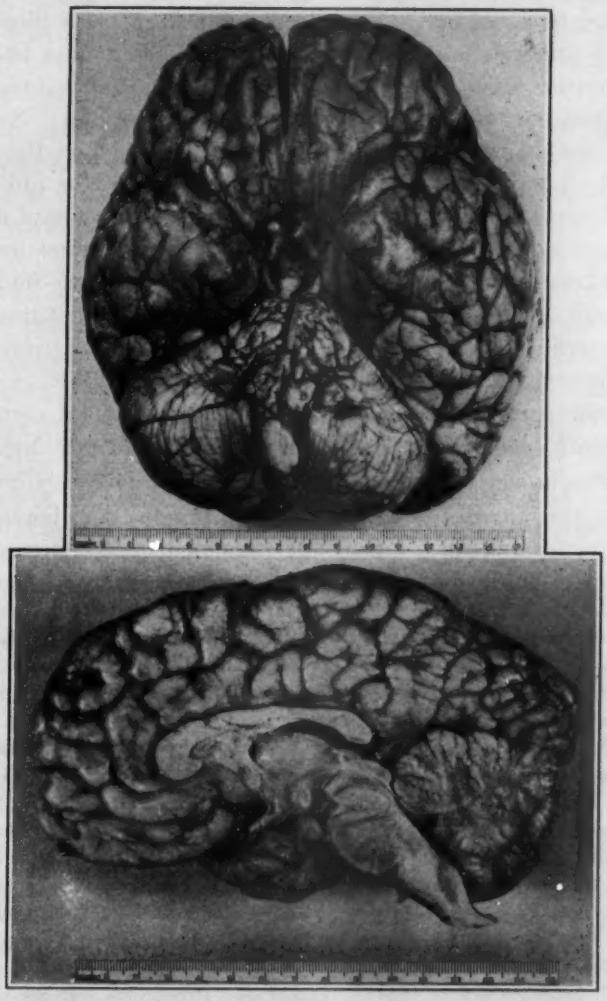

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Microscopically, the thymus had a well developed cortex and showed no evidence of acute degeneration of thymocytes. The lymph nodes showed normal structure, with large germinal centers in the follicles undergoing slight acute destruction of lymphocytes. The splenic follicles had large active germinal centers, as did Peyer's patches in the ileum. The aorta measured 3 cm. in circumference.

Comment.—After the absence of an ovarian neoplasm had been demonstrated at laparotomy, the clinical diagnosis could only be one of a diencephalic anomaly, either "idiopathic" or, less likely, in the nature of a tumor. A hypothalamic mass *was* observed at autopsy. It was not a true neoplasm but a congenital hyperplastic abnormality, a so-called hamartoma, arising from the tuber cinereum. Seven such instances, not counting our own, have been reported in the literature since 1931 (3 boys and 4 girls [9]); the present case is the fifth of a girl. Onset of symptoms usually occurred in the first few years of life.

The pathogenesis of these and other so-called cerebral instances of sexual precocity was reviewed in 1941 by Weinberger and Grant.[10] More recent experimental and clinical evidence (Bustamente [11]; de Lange [12]) seems to suggest that the tuber cinereum is an activating center of sexual behavior and maturation which might be inhibited by centers in the posterior part of the hypothalamus and the cerebral cortex. Precocious sexual development could then be brought about by hypothalamic abnormalities on one of four pathways: (1) direct nervous stimulation to activity of the anterior lobe of the pituitary by a hypoplastic mass appended to the tuberal centers; (2) hormonal hyperneurosecretion by such a hyperplasia stimulating the anterior part of the pituitary and/or

9. (*a*) Heuyer, G., and Vogt: Un cas de macrogénitosomie précoce, Arch. de méd. d. enf. **33**:737, 1930. (*b*) Le Marquand, H. S., and Russell, D. S.: A Case of Pubertas Praecox (Macrogenitosomia Praecox) in a Boy, Associated with a Tumor in the Floor of the Third Ventricle, Roy. Berkshire Hosp. Rep. 1934-1935, p. 31. (*c*) Driggs, M., and Spatz, H.: Pubertas praecox bei einer hyperplastischen Missbildung des Tuber cinereum, Virchows Arch. f. path. Anat. **305**:567, 1939. (*d*) Clark, W. E. L.; Beattie, J.; Riddoch, G., and Dott, N. M.: The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects (Henderson Trust Lectures), London, Oliver & Boyd, 1938, p. 180. (*e*) Gross, R. E.: Neoplasms Producing Endocrine Disturbances in Childhood [case 7], Am. J. Dis. Child. **59**:579 (March) 1940. (*f*) Bronstein, I. P.; Luhan, J. A., and Mavrelis, W. B.: Precocious Puberty Associated with Hyperplastic Abnormality of Tuber Cinereum, ibid. **64**:211 (Aug.) 1942; correction, ibid. **64**:723 (Oct.) 1942. (*g*) Hooft, C.; Dierickx, K., and Cieters, P.: Brain Tumor and Precocious Puberty, Maandschr. v. kindergeneesk. **12**:no. 4, 1943.

10. Weinberger, L. M., and Grant, F. C.: Precocious Puberty and Tumors of the Hypothalamus, Arch. Int. Med. **67**:762 (April) 1941.

11. Bustamente, M.: Experimentelle Untersuchungen über die Leistungen des Hypothalamus, besonders bezüglich der Geschlechtsreifung, Arch. f. Psychiat. **115**:419, 1942; Deutsche med. Wchnschr. **68**:289, 1942.

12. de Lange, C.: Zur Klinik und pathologischen Anatomie der hypothalamischen Form von Pubertas praecox, Ann. pædiat. **161**:113, 1943.

the gonads; (3) direct nervous stimulation of gonadal activity via tuberospinal connections; (4) disinhibition of the tuber cinereum by a lesion in the posterior portion of the hypothalamus. Whether the trigger mechanism acting through any one of those pathways be truly "cerebral," i. e., due to a pathologic brain lesion, or rather "idiopathic," i. e., genetically induced, is often difficult to decide on purely clinical considerations. De Lange [12] was inclined to expect an anomaly of the tuber cinereum in all "idiopathic" cases. Whether this is correct or not, one would indeed hesitate to make a quick diagnosis of the "idiopathic" type of precocious sexual development in view of the patient of Thoms and Hershman [13] and of Gesell and his co-workers [14] in whom the interval between the onset of female precocity and the onset of other signs and symptoms of a fatal astrocytoma of one cerebellar hemisphere was almost seventeen years.[15]

As to our patient's hormonal findings, excretions of estrogens in two premenstrual urinary specimens were unexpectedly low. This had made unlikely a preoperative diagnosis of an ovarian cyst or granulosa cell tumor, although such a child has been observed to excrete only 5 international units per liter of urine per day.[16] In our patient's condition of

13. Thoms, H., and Hershman, A. A.: A Case of Sexual Precocity, Am. J. Obst. & Gynec. **6**:349, 1923.

14. Gesell, A.; Thoms, H.; Hartman, F. B., and Thompson, H.: Mental and Physical Growth in Pubertas Praecox: Report of Fifteen Years' Study of Case, Arch. Neurol. & Psychiat. **41**:755 (April) 1939.

15. Since the publication of the review of one of us (H. P. G. S.) in 1946[1] the following 10 verified instances of sexual precocity associated with nonpineal hypothalamic lesions were found in the literature (6 in boys and 4 in girls): A. *Tumors:* (*a*) Scotti, D. W.: Malignancies in Infancy and Childhood, New York State J. Med. **39**:1188, 1939. (*b*) Poston, H., and Barber, A. H.: External Genital Hypertrophy in Infancy, Lancet **1**:384, 1942. (*c*) de Lange.[12] (*d*) Hooft, Dierickx and Cieters.[9g] (*e*) MacMahon, cited by Thannhauser, S. J.: Common Pathogenesis of Neurofibromatosis and von Recklinghausen's Osteitis Fibrosa Cystica, Medicine **23**:105, 1944. (*f*) Herlant, M.; Dubois, R., and Ectors, L.: Un cas de macrogénitosomie précoce, Ann. d' endocrinol. **6**:137, 1945. (*g*) Papez, J. W., and Ecker, A.: Precocious Puberty with Hypothalamic Tumor (Infundibuloma): Case Report, J. Neuropath. & Exper. Neurol. **6**:15, 1947. B. *Inflammations*: (*h*) Thomas, A., and Schaeffer, H.: Un cas de macrogénitosomie précoce avec hydrocéphalie, lésions inflammatoires de la région infundibulo-tubérienne et symphyse cervicale triméningée, sans néoplasme intracranien, Rev. neurol. **2**:595, 1931. (*i*) Hellner, H.: Ueber Pubertas praecox, im besonderen die hypothalamische Form, Med. Klin. **2**:1619, 1936. (*j*) Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944. (*k*) Ford, F. R., and Guild, H.: Precocious Puberty Following Measles Encephalomyelitis and Epidemic Encephalitis, with Discussion of Relation of Intracranial Tumors and Inflammatory Processes to Syndrome of Macrogenitosomia Praecox, Bull. Johns Hopkins Hosp. **60**:192, 1937. The present observation is the fourteenth recorded in a girl; the known total in boys to date is 30.

16. Stabler, F., and Thomson, J. G.: Precocious Puberty and Ovarian Granulosa Cell Tumor, J. Obst. & Gynaec. Brit. Emp. **47**:199, 1940.

demonstrated "cerebral" sexual precocity, one might have expected an estrogenic excretion of 100 to 300 international units per day as is normal for adolescent girls and young women. However, low figures for urinary estrogens have occasionally been encountered in serial examinations of similar patients (e. g., Gross [9e]). The reason for this might have been the fact that specimens of urine were obtained toward the end of the menstrual cycle when such excretions, to judge from experiences in normal adolescent girls, may drop to a daily level near 20 international units (Nathanson and his associates [17]).

An increase in estrogen catabolism must also be considered in the present patient. The finding of lack of urinary excretion of pregnandiol was in agreement with the absence at autopsy of luteinized tissue in the ovaries. Identical findings have been reported by Bronstein [9f] in a girl 22 months of age. On the other hand, there is on record the case of a 4½ year old girl with an unverified diagnosis of "cerebral" sexual precocity who did have a high excretion of pregnandiol and luteinizing effects in a biopsied ovarian specimen (Fisher [18]). Our patient's excretion of urinary 17-ketosteroids was high normal for her chronologic age. Correspondingly, the weight of her adrenals at autopsy was that of an average 7 year old girl and the cortices were thin, although the glomerulosa was actively proliferating. If the theory of Albright and other workers [19] of pituitary adrenocorticotropic stimulation of sexual hair growth is correct, these observations may explain the relatively late appearance and scanty amount of her pubic and axillary hair. The same would apply to the failure of the thymolymphatic system to involute (Evans [20]). Her growth spurt and skeletal maturation, besides being due in part to estrogenic activity, were indicative of increased production of both pituitary growth hormone and thyroid hormone, such as was also suggested by the microscopic appearance of the corresponding glands.

On the whole, this girl, at the age of 7, seemed to have attained that stage of adolescent pituitary-gonadal maturation in which the follicle-stimulating hormone had already aroused ovarian production of estrogen, while the activity of the luteinizing hormone, probably due to

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17. Nathanson, I. T.; Towne, L. E., and Aub, J. C.: Normal Excretion of Sex Hormones in Children, Endocrinology **28**:851, 1941.

18. Fisher, H. Z.: Precocious Menstruation, Am. J. Obst. & Gynec. **39**:525, 1940.

19. Albright, F.; Smith, P. H., and Frazer, R.: A Syndrome Characterized by Primary Ovarian Insufficiency and Decreased Stature, Am. J. M. Sc. **204**:625, 1942. Varney, R. F.: Kenyon, A. T., and Koch, F. C.: Association of Short Stature, Retarded Sexual Development and High Urinary Gonadotropic Titers in Women, J. Clin. Endocrinol. **2**:137, 1942.

20. Evans, H. M.: Recent Advances in Our Knowledge of the Anterior Pituitary Hormones, Am. Scientist **35**:465, 1947.

comparatively low estrogen levels, was not yet awakened. As in normal girls, this was the stage of unovulatory menstruations and "adolescent sterility" which normally covers from less than a year up to seven years (Montague [21]) following the menarche.

For an explanation of the patient's sudden and unexpected death, three possibilities may be discussed. In the first place, she may be looked at, in retrospect, as a poor operative risk because she had a brain tumor exerting slight pressure on neighboring parts of the hypothalamus. Second, the manipulation of her head and neck at the tooth extraction may have caused the heart to stop by way of the carotid sinus reflexes. Third, her endocrine disturbance, in association with the so-called status thymicolymphaticus, may have played an eitologic role.

CASE 2.—Arthur de S. was a white boy born Oct. 20, 1939.[22] The boy's father was 38 and his mother 30 years old as of 1948. Both were in good health but of short stature (5 feet [152.4 cm.]). They were of Italian and Swedish extraction, respectively. The father had many small brown areas and vitiligo spots on his trunk, predominantly on the right side. The mother had a number of small elevated pigmented moles on her neck and over the epigastric region. Her menarche had occurred at 11 years. The father had started shaving at 17 years. There were no known familial diseases, particularly no precocious sexual maturation. As of 1948, the patient had 3 brothers all in good health, free from cutaneous lesions or other anomalies and of average size and maturation for their age (the oldest, 12 years of age, weighed 29.7 Kg. and was 138 cm. tall; the second, 10 years of age, weighed 31.5 Kg. and was 134 cm. tall, and the youngest, 1½ years old, weighed 12.5 Kg. and was 85 cm. tall). The patient was born normally, at full term, weighing over 10 pounds (4,536 Gm.) and measuring 21 inches (53 cm.). He cut his first teeth at 7 months and started walking at 12 months and talking at 2 years. There were no headaches, dizziness or visual disturbances at any time but, on occasions, he complained of soreness of the eyes. His tonsils and adenoids were removed at 5½ years of age. At the same age he started shedding teeth and several were pulled. It was some time after these two events that this previously average-sized child (39½ pounds [17.9 Kg.] at 3 years; 50 pounds [22.7 Kg.] and 47½ inches [120.7 cm.] at 5½ years) suddenly started to grow rapidly. At about 7 years of age he was equal in height to his 10 year old brother, and at 7½ years he was 2 inches (5 cm.) taller than he. His total gain in the preceding two years was said to have been 1 foot (30.5 cm.) in height and about 20 pounds (9.1 Kg.) in weight. Starting at the age of 6¾ years, he displayed a tremendous appetite and his genitalia were observed to enlarge, pubic hair appeared, his strength increased and his voice deepened. Shortly after his eighth birthday facial hair appeared and pigmentation of the genital area increased. Several brown spots appeared on his skin between the ages of 7½ and 8½ years, and small purplish areas arose at the end of that period over his back and arms. At nearly 9 years of age he attended school in the third grade.

21. Montague, M. F. A.: Adolescent Sterility in the Human Female, Human Fertil. **11**:33, 1946.

22. These patients (cases 2 and 3) were seen through the courtesy of Dr. A. T. Kenyon, Department of Medicine, University of Chicago. We are also indebted to Dr. A. H. Parmelee, of Chicago, for communicating to us his findings in case 2.

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In March 1947, at the age of 7½ years, he was examined by Dr. A. H. Parmelee at Presbyterian Hospital, Chicago, whose clinical findings were in accord with our own three weeks later. Neurologic examination and roentgenograms of the skull showed no abnormality; the prostate was found to be large, and the skeletal age was advanced to 12 years. His serum sodium was 142.5 milliequivalents per liter. The intravenous pyelogram seemed to indicate large kidneys with moderately dilated calyxes and pelves which, together with a urinary excretion of 6.4 mg. of 17-ketosteroids per day, were then thought to suggest an abnormality of the suprarenal cortices.

Physical Examination.—The patient was observed in the clinics and hospital at 7 7/12 years (May 1947), 8½ years (April 1948) and 8 10/12 years of age (August

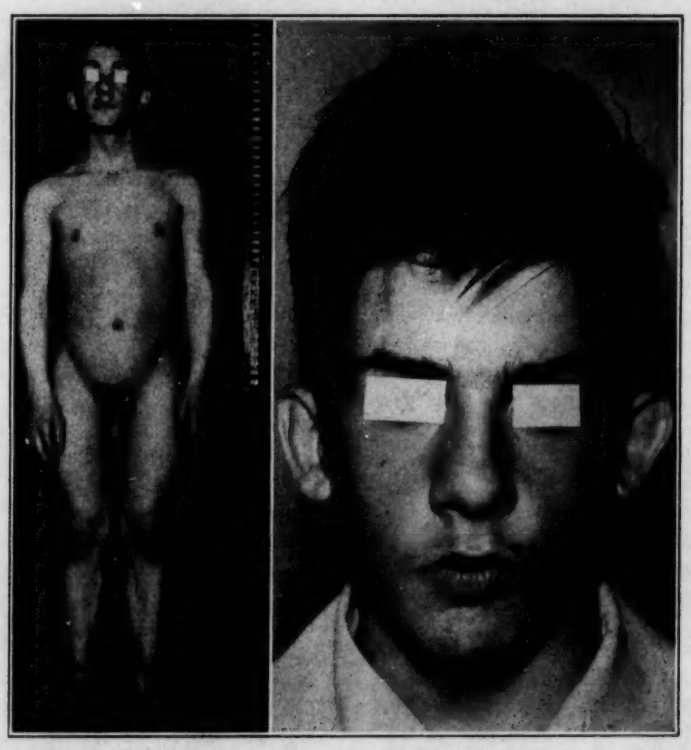

Fig. 4 (case 2).—Boy 7 7/12 years of age (left) who showed isosexual precocity associated with neurofibromatosis (von Recklinghausen's cutaneous syndrome, fig. 5, upper part) and a calcified lesion in the hypothalamus. Adolescence was near completion. Note swelling of nipples and ability to look upward. On the right is the same boy at 8 10/12 years of age. Besides facial hair and acne, note asymmetry of face and ear folding.

1948). On the first occasion his physical appearance resembled that of a short, stocky, athletic adolescent about 15 years of age (fig. 4, left). For his chronologic age he was tall (132.5 cm.) and heavy (33.6 Kg.). There were abundant scalp hair and a full escutcheon of pubic hair with a horizontal border. No axillary hair was noted, but hair was present on his lower legs. His voice was deep. His nipples were "budding." Both penis and testes were greatly enlarged but otherwise normal. The prostate was enlarged for his age. The blood pressure

was 120 mm. of mercury systolic and 70 diastolic. No anomalies of the skin were noted at this time. Results of neurologic examination were completely normal, including extraocular and intraocular movements. Roentgenograms of bones were not repeated. A determination of urinary 17-ketosteroids yielded 11.5 mg. in twenty-four hours. A diagnosis of precocious macrogenitosomia, presumably on a hypothalamic basis, was made.

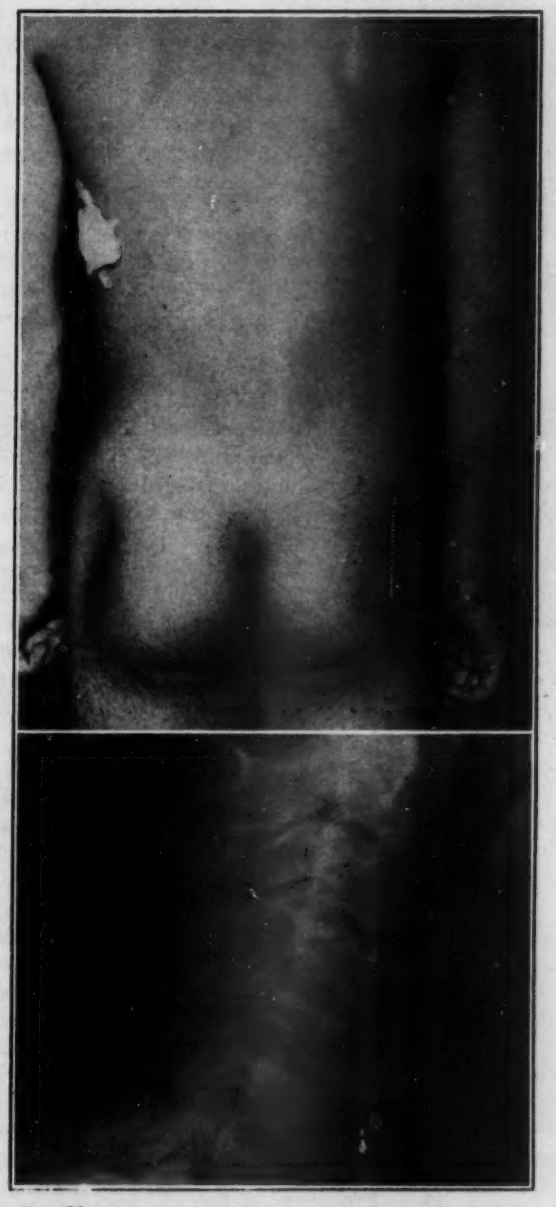

Fig. 5 (case 2).—Upper part, same boy at same age as in figure 4 (right). Note terminal hair, large café au lait spots and small neurofibromatous nodules. The lower part shows fuzziness and partial decalcification of the body of the sixth cervical vertebra (fibrous dysplasia?).

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On his second examination, at the age of 8½ years, he measured 142 cm. and weighed 42.6 Kg. His appearance and findings had changed little. There was fine facial hair of beardlike distribution but no axillary hair as yet. Typical café au lait spots were now present over his back, buttocks and chest, and on his trunk, upper arms and thighs there were numerous smooth, flat irregular spots of pale purple, up to 1 cm. in diameter (fig. 5, upper part). A slit lamp examination of the eyes revealed multiple small nodules in both irises which were diagnosed as disseminated neurofibromas. His fundi were normal but his visual fields were reduced. Neurologic examination once more gave normal results. The blood pressure was 120 systolic and 70 diastolic. His skeletal age reached a maximum of 14 to 15 years, the secondary epiphyses to the iliac crests and ischiac tuberosities being present. His dental age by roentgenologic examination was only 8 years. A diagnosis of neurofibromatosis (von Recklinghausen's skin disease) involving the irises and, possibly, the hypothalamus was entertained.

The third time the patient was hospitalized was at the age of 8 10/12 years. He was 146 cm. tall and weighed 41 Kg. (two months before, he had reached 43.6 Kg.). The circumference of his head was 56 cm. and the circumference of the chest 72 cm. His appearance was still more masculine than the year before. The shoulder girdle was broad and the muscles abundant. His facial hair was pronounced (fig. 4, right), and there were seborrhea and acne on his face and back. The nipples were still prominent. His pubic hair extended up the linea alba. A slight growth of axillary hair had made its appearance. His sexual organs were like those of a 16 year old boy. Measurements of the dorsal length of the flaccid phallus averaged 8 cm.; its circumference was 11 cm. The size of the testes was 5 by 3 cm. The prostate was corresponding in size. In contrast to the advanced sexual maturity, his dental eruption age was only 9½ years, there being 6 deciduous and 14 permanent teeth besides 4 empty premolar spaces. Similarly, he behaved on quite an infantile level and was shy, fidgety, apprehensive and tense. He showed no abnormal sex interest. The average mental age was exactly 7 years, the intelligence quotient being 80. This was considered a minimal rating. In search for minor congenital anomalies a moderate hypoplasia of the left side of his face which caused considerable asymmetry was noticed; his left ear was less folded than the right (fig. 4, right). There also were hypoplasia of the dental enamel and a high narrow-vaulted palate with overbite. He had only one transverse line in his right palm.

Laboratory Data.—Biochemical findings during hospitalization are listed in tables 1 and 2. Results of his routine urine and blood examinations were always negative, with the exception of high hemoglobin and red cell concentrations (16 Gm. per hundred cubic centimeters; 5,230,000 red blood cells). The Wassermann reaction of the blood was negative. The urea clearance was 75 per cent of average normal, and the insulin tolerance and Kepler-Power diuresis tests gave normal values. His caloric intake was 2,570 per day. Retrograde pyelograms revealed no anomalies. There were definite roentgenologic signs at the base of the skull. While the sella was normal, the left clinoid processes were disfigured, the anterior one being blunted and further from the middle than the right, the posterior one much sharper than the right. There also was unmistakable evidence of a calcification, covering a pea-sized area, about 1 cm. above the posterior clinoid processes. No calcifications were present in the pineal area. Normal visual fields were obtained at this time. Maximum skeletal age was observed to be 15 to 16 years. There was fusion or beginning fusion of epiphysial lines in the terminal phalanges, elbow, hip bones, femoral head and trochanters. Frontal and sphenoid sinuses were barely discernible. Dental age by roentgenologic examination was about 10 years. The body of the sixth cervical vertebra was fuzzy in outline and

partially decalcified but did not suggest a cyst; "subchondral necrosis," "osteochondritis" and a developmental variation were offered for diagnosis (fig. 5, lower part). There were no cysts in the skeleton anywhere. Roentgenograms of the chest revealed no abnormality. A testicular biopsy specimen showed maturation to the level of a young adult with active spermatogenesis and interstitial cell development. Biopsy of the skin confirmed the presence of typical neurinomas.

Treatment.—No attempt was made to influence the hypothalamic lesions which, prognostically, would hardly seem to be expanding in nature. Estrogenic therapy and concomitant metabolic studies were undertaken.

Comment.—In view of the patient's (familial) von Recklinghausen's syndrome, consisting of pigment spots and neurofibromas of the skin, similar tumors in the irises and possibly a "fibrous dysplasia" of a vertebral body, it did not seem unreasonable to interpret the calcifying lesions at the base of the brain in terms of neurofibromas in the region of the hypothalamus, more precisely of the tuber cinereum. Similar observations of sexual precocity associated with neurofibromatosis have been presented by several authors in boys and girls,[23] including such conditions as tuberous sclerosis and osteitis fibrosa cystica disseminata or McCune-Albright disease (footnote 23 *a* and *g*, autopsies). If the calcified tissue in the anterior portion of the hypothalamus were part of an expanding pineal neoplasm, one would have expected similar calcifications in the region of the pineal body itself. An adrenocortical hyperplasia or neoplasm was unlikely because of the complete maturation of the testes, the repeatedly normal pyelograms and the "normal" adult male level of urinary excretions of 17-ketosteroids.

This boy was born normal and had developed regularly up to the age of about 6 years. Pathogenetically, the earliest lesions in the hypothalamus that caused abnormal body growth and sexual precocity must have developed at that age, although the first cutaneous lesions of neurofibromatosis were observed only between 7½ and 8½ years of age. The hypothalamic lesions demonstrated in the area of the tuber

23. (*a*) Krabbe, K. H.: La sclérose tubéreuse du cerveau (maladie de Bourneville) et l'hydrocéphalie dans leurs relations avec la puberté précoce [case 1], Encéphale **17**:281, 437 and 496, 1922. (*b*) Mallam, J.: A Case Illustrating the Association of Recklinghausen's Disease with Derangement of Internal Secretion, Brit. J. Dermat. **34**:239, 1922. (*c*) deVries, H. F.: Case of Precocious Puberty Due to Pituitary Tumor and Recklinghausen's Disease, Nederl. tijdschr. v. geneesk. **74**:2001, 1930. (*d*) Sainton and Bailliart, P.: Syndrome fruste de Recklinghausen, macrogénitosomie précoce et glaucome, Bull. Soc. d'opht. de Paris, p. 69, 1932. (*e*) Lange, K.: Zur Ostitis fibrosa generalisata (Recklinghausen), Zentralbl. f. Chir. **65**:2368, 1938. (*f*) Falconer, M. A., and Cope, C. L.: Fibrous Dysplasia of Bone with Endocrine Disorders and Cutaneous Pigmentations (Albright's Disease), Quart. J. Med. **35**:121, 1942 (note the boy, case 1). (*g*) Footnote 15*e* (Albright's original case). (*h*) Barta, L.: Pubertas praecox, bedingt durch Neurofibromatosis generalisata (Recklinghausensche Krankheit), Ann. pædiat. **170**:15, 1948. An unpublished observation, similar to that of case 2 was made earlier at the Children's Hospital, University of Chicago.

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cinereum must have aroused activity of the anterior lobe of the pituitary. That activity, through the gonadotropic hormones, led to complete precocious maturation of testicular function and, through adrenocorticotropic stimulation, to production of additional adrenal androgens, thus causing almost complete virilization of the body, a considerable growth spurt and maturation of the skeleton. While his initial growth spurt was forceful, his present "adolescent" height was 2 inches (5 cm.) short of 5 feet (152.4 cm.) and, to judge from his skeletal maturation, not much more growth in height was to be expected. It must be remembered, however, that both his parents were only 5 feet tall. The estrogenic stimulation of the mamillae, probably also due to adrenocortical function, was part of the condition frequently observed in normal adolescent boys. The comparatively late appearance of axillary hair could not be explained; a lack of local tissue response to the circulating androgens has to be considered (Wilkins[24]).

As in the preceding and the following patients, this boy's mental and dental maturation were on the chronologic rather than the biologic age level. The multiplicity of congenital abnormalities was noteworthy (cf. cases 3, 5 and 6).

CASE 3.—Edwin M., a white boy, was born April 18, 1945. In 1947, his father was 42 years old and his mother 35, both in good health. There were no siblings. Several male members of the mother's family were tall. The mother had had her menarche at 14 years. No instances of sexual precocity were known on either side of the family. The child had been delivered by forceps at the Chicago Lying-In Hospital. No injury at birth was recorded, and on examination of the newborn infant nothing abnormal had been noted about the genitalia. The weight at birth was 4,415 Gm. and the height at birth, 56 cm. The baby sat up at 6 months, walked alone at 13 months and began to talk at about 18 months of age. No serious illnesses had occurred. To the mother, the infant's penis had first seemed large at the age of about 2 years. Shortly before that he had been examined by Dr. Swanson[25] who had observed a pronounced genital development, proportionate to the large size of the child's body. At 2 years of age, the weight was reported to be 18.9 Kg. and the height, 95.5 cm. At 2½ years there could be no reasonable doubt any longer of the excessive development of the boy's genitalia. When he was almost 3 years old, the mother noticed the first down of pubic hair. There was no history of headaches, vomiting, convulsions, unsteadiness or visual disturbances.

Physical Examination.—The boy was seen in consultation at the Bobs Roberts Hospital in November 1947 and June 1948, at the ages of 2 7/12 and 3 3/12 years, respectively. He had the appearance of a 5 to 6 year old boy. On the two occasions, his weight was 21.6 and 25.0 Kg. and his height 105 and 114.5 cm. The circumference of his head was 55 cm. His face appeared rather large, especially about the jaws (fig. 6). He had 21 deciduous teeth (one supernumerary right maxillary incisor), all liberally spaced in somewhat enlarged jaws.

24. Wilkins, L.: Abnormalities and Variations of Sexual Development During Childhood and Adolescence, Advances Pediat. **3**:159, 1948.

25. Dr. W. W. Swanson, of Chicago, gave us this information.

His left second toe was displaced upward. His external genitalia were the size of a 12 to 15 year old boy's; the penis measured 7 cm. in both dorsal length and circumference, and the testes were 3 and 4 cm. in longest diameter at successive examinations (fig. 7, left). There was no tumor in either testis. Pubic hair was absent at first, but a fine blond down had appeared during the interval between his first and second visits. Axillary hair was not present. No prostate tissue was palpable. The voice was not deep, and there was no facial seborrhea or acne. No masses could be palpated in the abdomen. His blood pressure was not determined. There was no diastasis of the sutures of the skull and Macewen's sign

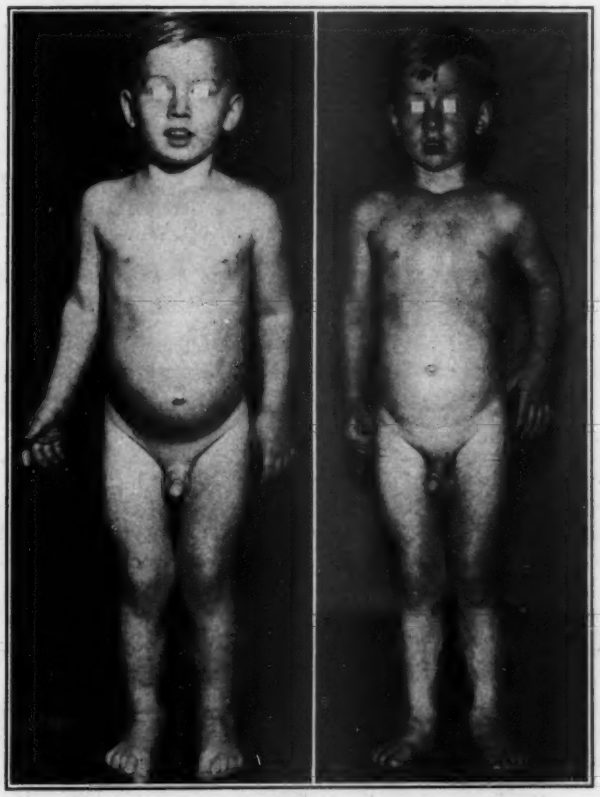

Fig. 6 (case 3).—Boy at 2 7/12 years of age on left, with isosexual precocity, presumably due to hypothalamic abnormality. Note large penis and testes without pubic hair. The same boy at 3 3/12 years of age is on the right. Note change in somatic proportions.

was absent. The optic fundi were perfectly normal and so were the extraocular and intraocular movements, especially the upward movement of the eyes.

Laboratory Data.—Roentgenograms of the skull showed a normal sella, no intracranial calcifications, no increased digital markings or diastasis of the sutures. The spheno-occipital juncture was open. The frontal and sphenoid sinuses showed beginning aeration. Skeletal age was estimated by Todd's standards of the hand to be 5½ to 6½ years. His dental age on roentgenologic examination was 2½ to 3 years. Two intravenous pyelograms were normal. Results of routine urine and

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blood examinations were noncontributory. Analyses of three day specimens of urine for 17-ketosteroids are listed in table 2. Psychologically, he behaved on the 3 year level, although he was mentally superior (mental age, 4½ years; intelligence quotient, 147).

No treatment was proposed at this time. The prognosis seemed to be necessarily in doubt for an indefinite period.

Comment.—The considerable overgrowth of the boy's testes, apart from that of the phallus, was suggestive of a hypothalamic anomaly, either "idiopathic" or tumor-like in nature. While lack of neurologic findings by no means excluded the latter, it was too early to diagnose the former. Hyperplasia of adrenocortical tissue, possibly in both testes, was rendered unlikely by the relatively low level of urinary 17-ketosteroids and the initial absence of pubic hair. The suggested hypothalamic anomaly, then, had aroused enough gonadotropic activity of the anterior lobe of the pituitary to cause testicular growth to the level of about 15 years, but the androgenic activity of the testes, and/or the adrenal cortices, was still on the level of 6 to 10 years. However, owing to the extreme sensitivity of young children to untimely stimulation by sex hormones (Nathanson and Aub[7]) that level of androgens, in conjunction with an oversecretion of the growth hormone, seemed sufficient to increase the boy's stature and skeletal age by several years, make his penis grow and provoke the first appearance of a pubic down at the age of 3.

Case 4.—Jay S. was a white boy born Jan. 26, 1942. The patient's parents in 1947 were in their early thirties, of good health and of average size. There were two sisters, one almost 8 years old and the other a young infant, both normal and healthy. On examination, the older sister showed no signs of precocious sex development, weighed 27.6 Kg. and was 129 cm. tall. She had begun to shed deciduous teeth at 5½ years. The family history was normal with respect to sexual development. The patient was born spontaneously at full term, weighing 3,200 Gm. He cut his first tooth at 6 months, sat up at 7 months, spoke his first words at 1 year and walked alone at 15 months. Since the age of 1 year, it was apparent that he rapidly outgrew his playmates, and later on, his older sister. At 1 year he weighed 11.3 Kg., at 2½ years, 17.3 Kg. His penis was said to have grown steadily in size after birth. Pubic hair was first noted at 2 11/12 years, axillary hair shortly before his fifth birthday. At this time he failed to be admitted to kindergarten because he was not yet 5 years old. At a little over 3 years of age he supposedly ate more than his father. He began shedding teeth at 5 years. He never showed any particular sex interest. At about 3 years he had an abortive attack of whooping cough and at 4 years severe attacks of measles and chickenpox, all without cerebral complications.

Physical Examination.—The boy was observed at Bobs Roberts Hospital at 3 7/12 years of age (March 1945) and at 5 1/12 years (February 1947). At the former age he looked like a schoolboy of 6, weighing 20.8 Kg. and measuring 110 cm.; at 5 years of age he had the appearance of a young adolescent, weighing 34.5 Kg. and measuring 137 cm. (figs. 7, right, and 8). His body frame

Fig. 7.—Left, same boy (case 3) at same age as in figure 6 (right). Note proportionate enlargement of penis and testes and beginning growth of pubic hair. On the right is a boy 3 2/12 years of age (case 4) with adrenogenital syndrome, i. e., incomplete isosexual virilism, presumably due to androgenic hyperplasia (or adenoma?). Note disproportionate enlargement of penis in relation to infantile testes and small scrotum: so-called dissociated virilization.

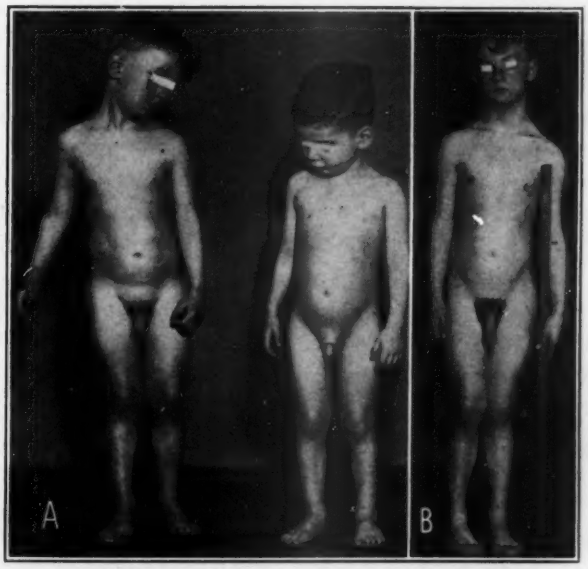

Fig. 8 (case 4).—*A*, left: Same boy at same age as in figure 7 (right). He is an "infant Hercules" with adult-sized phallus and some pubic hair. Right: Normal control, a boy of the same age. *B*, the same boy at 5 1/12 years of age. Note adolescent body, adult-sized phallus and infantile facial expression.

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and, particularly, his muscular system were greatly developed ("infant Hercules"). There were no congenital malformations or minor defects. His facial development and expression seemed rather gross and there was oiliness of the skin and typical acne later on. Axillary hair, facial down and deep voice were absent at 3 years of age but present at 5 years. There was some peripheral body hair at 5. Examination of the external genitalia revealed scanty pubic hair at 3 years and a full escutcheon with horizontal limitation at 5 years. The penis was anatomically normal but of spectacular size, measuring 12.5 cm. in dorsal length at 5 years of age. In contrast to its full adult development, the testes were completely infantile, measuring less than 2 cm. in length. The scrotum was small and slightly wrinkled (fig. 7, right). No tumors were palpable in the testes. The prostate was not examined. The abdomen and flanks were free from palpable masses. The blood pressure was 112 systolic and 70 diastolic at 3 years and 94 systolic and 46 diastolic at 5 years of age. Results of neurologic examinations were normal, including pupillary reflexes and extraocular movements. There were 20 deciduous teeth at 3 years of age and 16 deciduous and 2 permanent teeth at 5 1/12 years, which is normal for boys about 1 year older.

Laboratory Data.—Roentgenograms of the skull taken at 3 and 5 years of age showed a normal sella, no abnormal calcifications and a questionble minimal diastasis of the sutures. The spheno-occipital juncture was visible at 3 but not at 5 years of age. Frontal sinuses had just appeared by 5 years. Intravenous pyelograms were normal both times. Results of routine blood examinations and urinalyses done at 3 years proved noncontributory. The sedimentation rate was 5 mm. per hour. The blood Kahn and tuberculin reactions were negative. For biochemical data and urinary hormonal excretions, see tables 1 and 2. The boy's skeletal age was 10 to 11 years when he was 3 years old, the pisiform and epiphysis of the lesser trochanter being visible on the roentgenogram. At 5 years of age, on the basis of visibility of epiphyses in the iliac crests, his skeletal age was estimated to be 14 years. His dental age by roentgenograms agreed with his chronologic age. His intelligence quotient at the age of 5 was around 90 and his behavior was completely childlike.

Comment.—With this patient, a series of 3 is started who exemplified the so-called adrenogenital syndrome with precocious virilism. The present patient was the only boy in the series. In contradistinction to the preceding boys (cases 2 and 3), this patient's testes at the ages of 3 and 5 years were completely infantile, while the penis was of spectacular size with pubic hair growing at its base. This condition is known in boys as "dissociated virilism." Diagnostically, it pointed to an adrenocortical lesion rather than to a hypothalamic anomaly. Hormonal studies were confirmatory of this view. It is interesting to note that at 3 years of age the urinary 17-ketosteroid excretion (5 mg. per day) was high, but not excessively high for his chronologic age, whereas at 5 years, it had risen well above anything ever seen in normal adult men (45 mg. per day). In conjunction with the two years' clinical course and the repeatedly normal pyelograms, the low percentage of the beta-alcoholic fraction of the urinary steroids suggested a nonmalignant adrenocortical lesion, either hyperplasia or adenoma, be

it inside the adrenal glands or ectopic.[26] The structures of the boy's body that had reacted to overproduction of adrenocortical androgens were: phallus, scrotum, sex hair, sebaceous glands, larynx, skeleton including face?) and muscles. Even on the level of a urinary excretion of 5 mg. of 17-ketosteroids per day at 3 years of age, the effect of androgenic stimulation was remarkable, advancing as it did the "biologic age" for body size, skeleton and nongonadal sex characters to about 5½, 10 and over 13 years, respectively. This again may serve as an illustration that young children's organs are most responsive to relatively low levels of steroid hormones. The enormous progress in the boy's maturation during the following two years was, of course, due to the excessive androgenic production that had meantime developed. Signs or symptoms of adrenocortical insufficiency were at no time observed in this patient nor, for that matter, in the 2 succeeding girls (cases 5 and 6). Such instances have been reported by Wilkins and his associates,[27] Darrow [28] and Thelander.[29]

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26. Statistically, according to tabulation of one of us (H. P. G. S.[1]), adrenocortical adenoma may seem commoner than hyperplasia (without anatomic pseudohermaphrodism). However, it must be borne in mind that the tabulation lists only verified cases of either condition, and many a hyperplasia goes unverified. Since the aforementioned publication, the following 10 verified instances of adrenocortical hyperplasia without pseudohermaphrodism have come to our attention; 7 of them were of girls and 3 of boys, all of them virilized except 1 girl (Karnaky[9]): (*a*) Dahl-Iverson, E.: Adrenalectomy for Adrenogenital Syndrome in Children, Acta chir. Scandinav. **90**:210, 1944. (*b*) Luft, R.: Study on Hirsutism, Cushing's Syndrome and Precocious Puberty, Acta. med. Scandinav., 1944, supp. 149, p. 1; Hyperfunction of Adrenal Cortex in Children Before Puberty, Nord. med. (Hygiea) **27**:1773, 1945. (*c*) Boularan; Cahuzac; Salvador, and Genesseau: Macrogénitosomie et gynandrie chez un sujet porteur de deux tumeurs cortico-surrénaliennes incluses dans les ligaments larges, Ann. d'endocrinol. **6**:57, 1945. (*d*) McIntosh, C. B., and Brown, W. E.: Adreno-Genital Pseudohermaphroditism Treated with Stilbestrol, J. Pediat. **27**:323, 1945 (two sisters). (*e*) Karnaky, K. J.: Premature Sexual Precocity in a Young Girl, J. Clin. Endocrinol. **5**:184, 1945. (*f*) Mattar, A.; Correa, B. O., and Urrutia, C.: Early Sexual Development, with Report of Two Cases, Rev. chilena de pediat. **17**:305, 1946. (*g*) Bergman, B.: Sex Precocity and the Adrenogenital Syndrome, J. Pediat. **31**:142, 1947. (*h*) Broster, L. R.: The Adrenals in Sex, Practitioner **158**:307, 1947. (*i*) Wyllie, W. G.: Precocious Puberty of Suprarenal Origin? Proc. Roy. Soc. Med. **40**:154, 1947.

27. Wilkins, L.; Fleischmann, W., and Howard, J. E.: Macrogenitosomia Praecox Associated with Hyperplasia of the Androgenic Tissue of the Adrenal and Death from Corticoadrenal Insufficiency: Case Report, Endocrinology **26**:385, 1940.

28. Darrow, D. C.: Congenital Adrenal Cortical Insufficiency and Virilism, Yale J. Biol. & Med. **16**:579, 1944.

29. Thelander, H. E.: Congenital Adrenal-Cortical Insufficiency Associated with Macrogenitosomia: Follow-Up and Terminal Report, J. Pediat. **29**:213, 1946.

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The prognosis for boys with adrenocortical hyperplasia appears to be favorable. Partial adrenalectomy does not seem to be effective. The "incomplete" virilism will be completed at a normal adolescent age owing to the awakening of the proper hypothalamopituitary mechanisms. Adult body size may fall below normal average standards because of premature closure of epiphysial lines.

CASE 5.—Noreen M., a white girl, was born Jan. 18, 1940. The family consisted of a partially deaf mother 37 years of age with heart trouble and anemia and a healthy father 42 years of age. There were two healthy siblings, a girl of 10 and a boy of 4 years. No example of a similar abnormality was known in the family. Delivery was normal and at full term; the weight at birth was 2,750 Gm. The girl had always been a good eater and her motor and speech development were normal. She attended school in the second grade. She had uncomplicated measles at 5 years of age. At birth a large fold of skin just anterior to the urethral opening was noted. This enlarged disproportionately until, at the time of admission, there was a penis-like "growth" with no opening in it. Her voice had always been low pitched and her physique large and somewhat boyish. Her inclinations were toward playing with boys of her age. At about 5 years of age pubic hair developed which steadily grew to the present state. Her breasts had not grown and there were no menstruations. In March 1947, she was referred to Mercy Hospital.[30]

Physical Examination.—The patient was a 7 year old, stocky, muscular girl with a morphologic appearance definitely more feminine than masculine (fig. 9, left). Her weight was 31.3 Kg. and her height, 135 cm. Measurements of her hips were about those normal for a 9 year old girl. She had a broad, rather high face and a slight epicanthal fold. Her long, coarse scalp hair was arranged in braids and her eyebrows were heavy. There was a dark down on her upper lip and some peripheral hair on her outer thighs. About a dozen pigmented strands of axillary hair were present on the right side but not on the left. A single strand of hair had grown in the periphery of the areola of the right nipple. There was no trace of breast development. There was acne on her forehead and her voice was husky. Her external genitalia showed abundant coarse pubic hair with horizontal limitation. From this protruded a clitoris 3 cm. long and 1.5 to 2 cm. wide, with retractible foreskin. The urethral opening was about 0.5 cm. posterior to the base of the clitoris. There was no vaginal opening between the slightly wrinkled and redundant labia majora. No gonadal bodies were palpable in the labia or the inguinal canals. On rectal examination a midline body 3 to 4 by 1.5 to 2 cm. was palpated about 4 cm. up the rectum, but no adnexal structures were made out. No masses were felt in the abdomen or flanks. A harsh systolic murmur heard over the apex of the heart was independent of body position. Blood pressure readings averaged 103 mm. of mercury systolic and 73 diastolic. There were no neurologic signs or symptoms. Her mental age was equal to her chronologic age. She had all her permanent first molars and incisors, which gave her a dental eruption age of 8½ years.

Laboratory Data.—Roentgenograms showed the skull, including the sella, to be normal. Roentgenograms of the bones revealed the presence of the epiphyses of the

30. This patient was sent to us through the courtesy of Dr. H. W. Elghammer, of Chicago. The surgical staff of Mercy Hospital, Chicago, performed the operations.

acromion, coracoid process and the iliac crest and fusion in the medial epicondyle, indicating a skeletal age of 14 to 15 years. There was an aseptic necrosis in the head of the right second metatarsal (Freiberg's disease). Dental age by roentgenograms was about 7 years. Intravenous pyelograms were normal except for the left calyx system, which was on a level 1 to 2 cm. lower than the right. Routine urine and blood tests showed nothing abnormal. For results of biochemical and hormone studies, see tables 1 and 2.

Operations, Course, Treatment.—The patient was operated on twice at Mercy Hospital. In April 1947, a pelvic laparotomy revealed normal infantile female

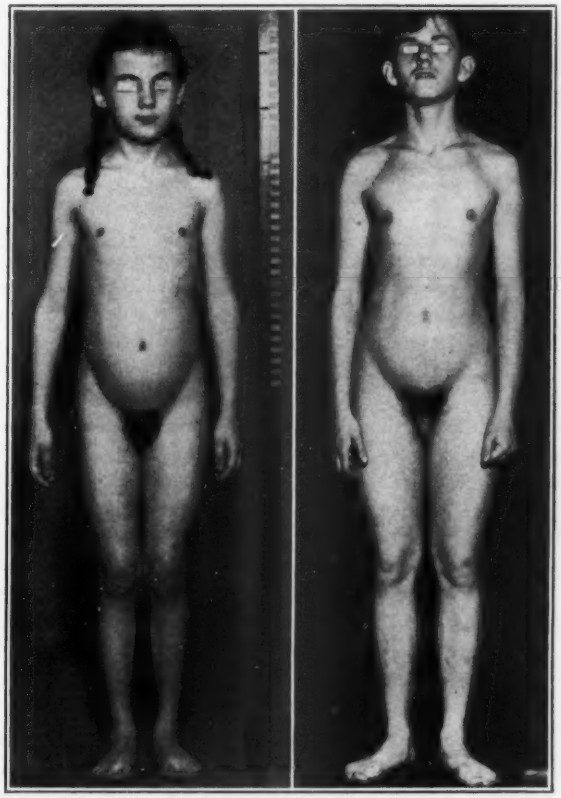

Fig. 9.—Left, girl (case 5) 7 2/12 years of age with female pseudohermaphrodism and precocious virilism (adrenogenital syndrome) due to presumable embryonal androgenic hyperplasia (no adenoma was present). Note enlargement of clitoris. Right, genetic girl ("Richard," case 6) 9 2/12 years of age with female pseudohermaphrodism and precocious virilism (adrenogenital syndrome) due to presumable embryonal androgenic hyperplasia. Note wide feminine hips in masculine adolescent body.

genitalia. There were no mature follicles or corpora lutea noticed in the ovaries, either on gross inspection or microscopically in biopsy sections. In May 1947, the adrenals were explored by the dorsal approach. Both glands were exposed to inspection and the left to palpation. They appeared to be "normal" as far as size and consistency were concerned and did not contain any neoplasms. Attempts

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to obtain specimens for biopsy failed. The postoperative courses were uneventful. It was planned to do a vaginal plastic operation and partial resection of the clitoris later. Five to 10 mg. of diethylstilbestrol U.S.P. per day was suggested.

This case will be commented on together with case 6.

CASE 6.—"Richard" C., a white female, was born Dec. 6, 1935. The patient was the only child of healthy, divorced parents now in their early thirties; there had been two induced abortions. Nothing was known of precocious sexual development in either parental family. At full term delivery the infant weighed 2,950 Gm. Genital abnormalities were noticed at birth and interpreted as hypospadias in a male child ("Richard William"; photocopy of birth certificate was obtained). The baby was able to sit up at 6 months and to walk and talk a few words at 11 months. At 3 years of age pubic hair was said to have developed; the growth became fuller in the next three years. Axillary hair presumably made its appearance between 4 and 6 years of age and facial hair and deepening of the voice were noticed bewteen 8 and 9. From 5 to 7 years of age the child attended a boarding school and from 7 to 9 an ungraded class in public school. There was a report of measles, chickenpox and whooping cough without complications.

At the age of 4 1/12 years, the patient was admitted to Cook County Hospital, Chicago,[31] because "the penis was not normal." Among the physical findings were "a large penis (4 cm. in length), hypospadias and cryptorchidism (both testes undescended)." The weight was 22.7 Kg. and the height, 125 cm. Pubic hair was present. The skull and especially the sella were normal on roentgenographic examination, and an encephalogram and examination of the spinal fluid revealed nothing abnormal. The intelligence quotient was 78 and the mental age, 3 1/12 years. An intravenous pyelogram showed normally outlined kidneys and well formed calyxes and pelves bilaterally. On roentgenograms of the skeleton eight carpal bones were present; the patella was well developed, and a "slight fragmentation of the tibial tubercle" was suggested. These signs indicated a skeletal age of about 11 years. Some biochemical data are listed in table 1. The hemoglobin concentration was 75 per cent. No basal metabolic rate was taken.

"Richard" was brought to the urology clinic in January 1945 because at birth the mother had been advised that an operation on the "penis" should be performed at the age of 9 or 10 years. The same day the child entered Bobs Roberts Hospital with the understanding that the "penis" would be repaired in such a way as to rectify the feminine manner of urinating.

Physical Examination.—On first impression this 9 2/12 year old patient looked decidedly boyish, like an adolescent about 15 or 16 years of age (fig. 9, right). The weight was 48.2 Kg. and the height, 150 cm. The muscular system was greatly developed, the shoulder girdle broad and the voice deep. The face was coarse and covered with frontal acne, and a down of hair was present on the upper lip, chin and cheeks. There also was peripheral hair on the legs. Axillary hair was moderately developed. Pubic hair was present in abundance and a few strands were growing on the linea alba. As to the external genitalia (fig. 10, upper part), underneath a phallus too small for a penis and too large for a clitoris there were a perineal urethral opening and a perineal scrotum-like structure with a decided nonmucosal midline retraction but no vaginal opening. No gonadal bodies were palpable anywhere, nor was a prostate found on rectal examination. The hips were at once noticed to be well rounded and wide. There were 24 permanent teeth,

31. The administration of the Cook County Hospital conveyed to us the information here quoted.

corresponding to an eruption age of 11½ years. No masses could be felt in the abdomen or flanks. Blood pressure readings ranged about 110 mm. of mercury systolic and 68 diastolic. On neurologic examination there were no abnormal signs except a weakness of outward movement in the right eye and a fine nystagmus in both eyes on looking to the right and to the left. There was no limitation of convergence on upward movement in either eye and no abnormality of the pupillary reflexes. Visual fields and intracranial pressure were not grossly abnormal.

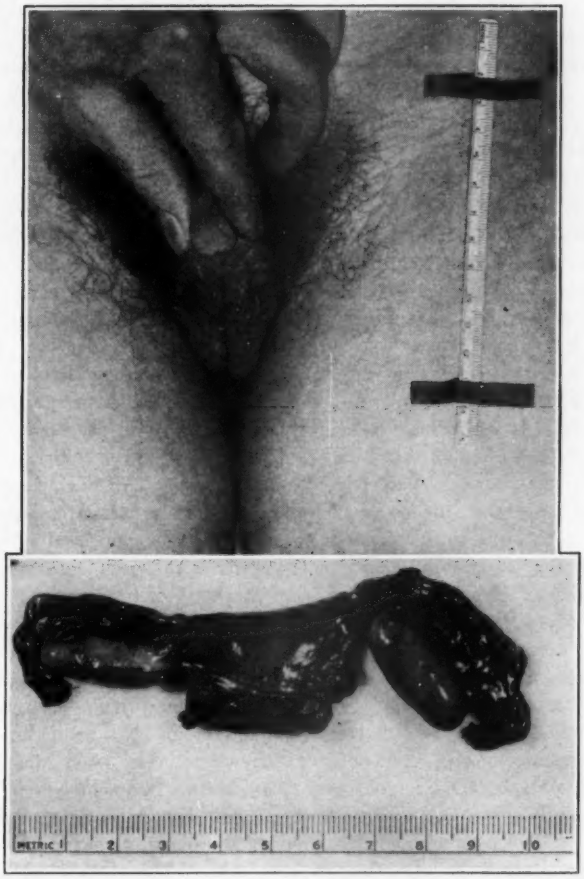

Fig. 10 (case 6).—The same child at the same age as shown in figure 9, right. Upper part, external genitalia include enlarged clitoris and urogenital sinus under well developed pubes. Lower part, operative specimen of complete set of infantile female internal genitalia.

Laboratory Data.—Roentgenograms of the skull showed a normal sella and a speck of calcium density in the position of the pineal body. Increased digital markings of the skull were noted. The spheno-occipital juncture was open. There were no frontal sinuses. Intravenous pyelograms were quite normal. In post-injection films, a round density 4 mm. in diameter lateral to the right renal calyxes was observed. Routine urine and blood examinations gave normal results. Kahn reactions of the blood were negative in 1940 and 1945. Results of an oral dextrose

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tolerance test ran a moderately elevated course: The level on fasting (?) was 146 mg.; at one-half hour, 206 mg.; at one hour, 140 mg.; at two hours, 121 mg., and at three hours, 96 mg., per hundred cubic centimeters. Other biochemical data are listed in table 1. Urinary excretions of 17-ketosteroids (table 2) were studied during the patient's entire hospitalization of six weeks, both preceding and following operation. Skeletal age was advanced to almost 20 years of age. The coronal suture of the skull was closing, but not the metopic one; the epiphyses of the iliac crest and of the sternal end of the clavicle were present. There was complete fusion of the epiphysial lines of most of the long bones, and the rib cartilages at the costal margin were ossifying. The dental age shown by roentgenograms was about 12 years. The intelligence quotient was 89 and the mental age, 7 $^{10}/_{12}$ years; there was an even duller impression during a psychiatric interview. An electroencephalogram was not suggestive of a tumor but did record waves slower than 8 per second. The patient displayed a definite masculine sex consciousness on a completely childlike level.

Operation and Operative Specimen.—The preoperative diagnosis was "undescended testes" with possibly some ovarian tissue present (ovotestis?). On Feb. 23, 1945, the right inguinal canal was explored but no testes were observed. The internal abdominal ring was opened and a round ligament traced. It could be readily seen after abdominal exploration that the patient possessed two ovaries, two tubes, a small uterus and a blind-ending vagina. A decision was made to remove these structures, and, through an additional long left rectus incision, complete castration was performed. The adrenals were not explored. The postoperative diagnosis was female pseudohermaphrodism with precocious virilism.

The operative specimen consisted of a uterus, two tubes with fimbriae, a right round ligament and two gonads (fig. 10, lower part). All organs appeared infantile. On the posterior surface of the left gonad there was a small cyst. Microscopically, the uterine muscle and endometrial surface appeared normal infantile. The gonads were examined independently by three different observers. There was agreement about the fundamentally ovarian character of both gonads. They showed many primordial, atretic and more or less immature graafian follicles typical of the gland of a 9 year old girl. Both ovaries contained follicular cysts. Adjacent to the fimbriae of each fallopian tube there were unusually large concentrations of tubular structures of mesonephric origin which might have been interpreted as either epoophoron and paroophoron or epididymoid. No testicular seminiferous tubules or spermatic cells were observed anywhere. The most unusual structures were two islands of cells which were seen in the ligamentous supports on the side of the right ovary within 5 to 10 mm. of its border. The cells were uniform, polyhedral and acidophilic and contained small amounts of pigment of the lipochromic type masked by the eosin of the stain. There was close association of the cells with the endothelium of blood capillaries. The question was whether these cellular clusters were to be interpreted as interstitial cells of Leydig or rather as adrenocortical cells. The evidence seemed to favor the latter hypothesis. In summary, there was overdevelopment of the epoophoron and paroophoron bilaterally and ectopic androgenic (adrenocortical?) tissue in the right mesoophoron.

Postoperative Course.—The patient made an uneventful recovery and was discharged three weeks after operation. The parents were informed about "his" true sex, but the patient was not, the understanding being that "he" should never know and would continue "his" boyish way of life which seemed so irrevocably established. Although the patient expressed disappointment over the failure of an operative correction of the urinating mechanism, there was now no desire to

undergo another operation for such repair. It was deemed advisable to wait until this desire was spontaneously uttered by the child. The family has since moved away from Chicago.

Comment, Cases 5 and 6.—These patients were examples of the "adrenogenital syndrome" with precocious virilism in genetic girls. Presumably owing to an embryonic hyperplasia and overfunction of the androgenic zone of the adrenal cortices, their external genital organs were malformed in the direction of pseudohermaphrodism, while the internal genitalia followed the true sex. The gonads and uterus were surgically demonstrated to be normal for an infantile female. This is statistically the most frequent situation.[32] The first patient (case 5) was easily recognized and, in fact, reared from birth as a girl, while the second (case 6) had always been taken for a "boy" afflicted with "hypospadias and undescended testicles." Hormonally, they had many points in common with the boy of case 4. Both patients excreted an unphysiologic excess of 17-ketosteroids in the urine (36 mg. and 20 to 53 mg. per day, respectively); there was a low percentage of the beta-fraction in the second patient (case 6). In both patients, at the ages of 7 and 9 years, respectively, the development of muscles and bones, as well as that of sexual hair, larynx and sebaceous glands, was well advanced into biologic adolescence. There were no signs of feminine secondary sexual characteristics in either child, with the exception of wide hips in the second (case 6). No reliable direct or indirect evidence of adrenal anomalies could be produced in either patient despite surgical efforts to that effect in the first. Yet there can be little doubt that both girls' conditions were due to a nontumorous hyperplasia of androgenic adrenocortical tissue either within the adrenals or outside. The possibility of ovarian arrhenoblastoma was excluded by direct exploration. No such case has ever been observed in a child below the age of 15.

The second child (case 6) had always been diagnosed as a boy. When "he" was first hospitalized at 4 years of age, "his" body weight, bone age and precocious virilism came close to that of the previous boy (case 4) when 3 years of age. When the child was again seen at 9 years of age, almost all observers took "him" to be a "boy," although some expressed doubt in view of the broad hips. As a cause of "his" virilism, the significance of the right parovarian clusters of adrenal-cortex-like cells (cf. the case of Boularan and his associates [26c]) could have been only slight, as is shown by the merely temporary drop in urinary 17-ketosteroid excretion after removal of those cells along with the ovaries. Moreover, castration as such, at least in the adult

32. There was no instance of sexual precocity among 8 cases of male pseudohermaphrodism and twenty-odd cases of hermaphrodism in Young, H. H.: Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases, Baltimore, Williams & Wilkins Company, 1937.

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of either sex, may bring about a temporary depression of urinary steroid excretion, the postcastrational rise being due to a presumable adrenocortical stimulation via the anterior lobe of the castrate pituitary (Friedgood [33]; Scott and Vermeulen [34]). But, in the first place, our patient was an immature female and, secondly, such pituitary stimulus in a castrate could not have brought the urinary excretion of 17-ketosteroids back up to a level of 38 mg. per day. This could have been done only by some extragonadal androgenic tissue presumably in the adrenal cortices.[35]

Finally, there was the finding of a calcification in the pineal area in the first patient (case 6). As long as the child was taken to be a boy, a diagnosis of pineal tumor seemed inevitable until proved to the contrary. The patient's high uric acid and low cholesterol levels in the blood also pointed in the direction of a hypothalamic lesion (Guterman [36]). However, even before laparotomy, indirect proof to the contrary was at hand, consisting in the child's pseudohermaphrodism and excessive levels of urinary steroid excretion, pineal tumors with sexual precocity having been reported only in normal boys who showed a moderate increase in steroid excretion. Strong evidence against a diagnosis of pineal tumor was furnished by the demonstration at laparotomy of the child's female sex. The pineal calcification, then, was to be explained as a physiologic phenomenon in a person of a "biologic age" of 18 to 20 years.[37] According to Dyke,[38] pineal calcification normally occurs in the first decade of life in 5 per cent of the

33. Friedgood, H. B.: Concerning the Biochemistry and the Physiological and Clinical Significance of the Sex Hormones and 17-Ketosteroids, in The Chemistry and Physiology of Hormones, American Association for the Advancement of Science, 1944.

34. Scott, W. W., and Vermeulen, C.: Studies on Prostatic Cancer: V. Excretion of 17-Ketosteroids, Estrogens and Gonadotropins Before and After Castration, J. Clin. Endocrinol. **2**:450, 1942.

35. According to recent studies in men and chimpanzees, one third of the total 17-ketosteroid excretion remains after total gonadadrenalectomy: Huggins, C. B., and Scott, W. W.: Bilateral Adrenalectomy in Prostatic Cancer, Ann. Surg. **122**:1031, 1945. Dorfman, R. I.; Horwitt, B. N.; Shipley, R. A.; Fish, W. R., and Abbott, W. E.: Metabolism of the Steroid Hormones: Studies on 17-Ketosteroids and Androgens, Endocrinology **41**:470, 1947. Speculation has arisen concerning the adrenocorticotropic origin of the cortical hyperplasia of the adrenogenital syndrome: Talbot, N. B.; Butler, A. M, and Berman, R. A.: Adrenal Cortical Hyperplasia with Virilism: Diagnosis, Course and Treatment, J. Clin. Investigation **21**:559, 1942. Bergman.[26g]

36. Guterman, H. S.: Personal communication to the author.

37. Calcifications of rib cartilage have been seen in a boy 11 9/12 years old with precocious virilism due to verified hyperplasia of the adrenal cortices by Mattar and his associates.[26f]

38. Dyke, C. G.: Indirect Signs of Brain Tumor as Noted in Routine Roentgen Examinations, Am. J. Roentgenol. **23**:598, 1930.

cases, in the second decade in 28 per cent and in adults over 40 years of age in about 60 per cent. Consequently, on the basis of "biologic age," our patient had about a 30 per cent chance to have a calcified pineal body.

No partial adrenalectomy was proposed for any of our 3 patients with adrenocortical virilism, since effects of surgical treatment have been shown to be slight in either sex. While the boys "grow into" and complete their virilism during physiologic adolescence, the prognosis for girls is less favorable, but estrogen therapy may prove of value. In our last patient it was decided not to reverse the "boy's" adopted sex for reasons of "his" psychologic fixation; therefore castration was performed.

SUMMARY AND CONCLUSIONS

Six examples of precocious sexual development are studied from the standpoint of diagnosis and pathogenesis. The differentiation of such abnormal sexual precocity from physiologic early sexual maturation is emphasized.

The first 3 patients belong to the "hypothalamic" group of sexual precocity.

The first patient in this group was a girl with almost complete isosexual precocity who was under observation from 5 to 7 years of age. There were no neurologic signs of an intracranial lesion. Unexpected death occurred in conection with surgical procedures. Pathologic examination revealed a pea-sized "hamartoma" of the tuber cinereum that was attached to the hypothalamus like a third mamillary body. Microscopically, it consisted of normal tuber cinereum cells the fibers of which extended, through an anterior peduncle, into the cerebral substance. The girl's ovaries contained mature follicles but no luteinized tissue. There was a "status thymicolymphaticus."

In the second patient in this group, a herculean boy observed between 7½ and 9 years of age, hereditary neurofibromatosis (von Recklinghausen's cutaneous syndrome), verified on biospy, and disseminated neurofibromas of the irises were observed. Calcifications were demonstrated behind and above the sella and thought to indicate the presence of neurinomas or neurofibromas in the area of the tuber cinereum. The boy's precocious virilism proved to be "complete" by the presence of adult-sized testes, biopsies of which confirmed a state of maturation seen in the young adult, including active spermatogenesis.

The last patient in this group was a boy 2½ to 3 years of age with a large phallus, greatly enlarged testes and the first down of pubic hair. Although there was no other evidence of an intracranial lesion, he was thought to belong to the hypothalamic group of sexual precocity. Whether this precocity was due to a slow-growing brain tumor or came under the title of the "idiopathic" or "constitutional" type, it is impossible to state at this time.

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In all 3 children of this group, the urinary excretion of 17-ketosteroids was increased for their chronologic age but not beyond what would have been normal for older children and adolescents or young adults. In two premenstrual specimens of urine collected in the girl the expected increase in estrogen excretion was not demonstrated. This would not seem to exclude increased production and metabolism of estrogens which, on clinical grounds, could not well be doubted. She excreted no pregnandiol.

It seems useful to emphasize the observation of a normal pituitary body or sella in all 3 patients. The demonstrated or suspected hypothalamic lesions could not have promoted the syndrome of sexual precocity if the anterior lobe of the pituitary had not been normal and ready prematurely to respond to abnormal diencephalic stimuli.

The remaining 3 patients are examples of the "endocrine" group of sexual precocity, more specifically, of the adrenogenital syndrome associated with precocious virilism. All 3 showed an excessive excretion of urinary 17-ketosteroids up to levels of 20 to 53 mg. per day.

The first patient in this group, a boy of 3 to 5 years of age, excreted only 5 mg. of 17-ketosteroids in the urine per day in the beginning of his sexual precocity; later on, at 5 years of age, the figure had risen to 45 mg. He was a perfect example of an "infant Hercules" with the body structure of a normal male. He also showed the remarkable phenomenon of "dissociated virilization," i. e., complete infantilism of the testes in the presence of an adult-sized phallus and pubic hair. Repeated intravenous pyelograms were normal. A surgical exploration was not permitted.

The second patient in this group was a girl, 7 years old. She had been born a pseudohermaphrodite, with persistence of the urogenital sinus. Her gonads were proved by surgical exploration to be of the female sex. In a second operation her adrenals were observed to be free from cortical adenomas and grossly "normal"; no biopsy specimens were obtained, however.

The last patient, 9 years of age, was a genetic girl but had been reared as a boy. The external genitalia resembled those of a hypospadiac boy with no palpable gonads in a mesially depressed scrotum. The hips appeared broad, but otherwise "his" physical and psychologic orientation was completely masculine. At laparotomy, a complete set of immature female genitalia was discovered and castration was carried out. The adrenal glands were not explored, but intravenous pyelograms had been unrevealing. The operative specimen showed infantile ovaries normal for the chronologic age and a few tissue clusters in the right parovarium consisting of adrenal-cortex-like cells. They did not prove hormonally to contribute to the patient's virilism.

All 3 patients in the second group are thought to be unverified examples of congenital hyperplasa of the androgenic tissue of the adrenal cortices and/or of some unidentified ectopic adrenocortical cells.

While, obviously, all patients in either group showed a higher or lesser degree of so-called macrogenitosomia, it was surprising to find the dental maturation and mental development of our patients rather close to the chronologic age and, therefore, out of step with the biologic maturation of the rest of the body. Tooth and brain tissue, then, seem to be relatively unresponsive to the premature circulation of more or less increased amounts of gonadal and adrenocortical sex hormones or other hormones directly or indirectly produced by the anterior lobe of the pituitary.

The problems of growth and maturation in our series of sexually precocious children will be the topic of the second part of this publication.

NOTE.—Since this paper went to press, 2 patients (case 3 and 4) were presented for reexamination. Their maturational progress will be reported in the second part of this publication. In May 1949, the boy (case 3), now 4½ years of age, still failed to show any localizing neurologic signs. His daily urinary creatinine excretion was 0.6 Gm. and his 17-ketosteroid excretion was 1.7 mg. The other boy (case 4) in April 1949, at the age of 7 3/12 years, showed normal intravenous pyelograms for the third time in four years. His daily urinary excretion of creatinine was 1.07 Gm., that of creatine, 0.22 Gm. and that of 17-ketosteroids, 62.6 mg.

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The Johns Hopkins Hospital (5) (Dr. Scott).

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APLASTIC ANEMIAS IN CHILDHOOD

Report of a Primary Idiopathic Refractory Type, with Splenectomy, in an Eleven Year Old Girl

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CHICAGO

PRIMARY idiopathic aplastic anemia is manifested by a profound anemia associated with leukopenia, neutropenia and thrombopenia and later by hemorrhagic tendencies and hypocellular bone marrow. It is an acquired disease of unknown cause occurring infrequently in childhood. In contrast to this type of the disease is a similar clinical entity due to a known etiologic agent and termed symptomatic or secondary aplastic anemia.

Ehrlich [1] in 1888 first described the occurrence of the condition under discussion and termed it aplastic anemia. Frank [2] in 1915 called the condition aleukia haemorrhagica. More recently Rhoads and Miller,[3] working on the effect of intensive therapy with liver extract, noted that certain cases of primary idiopathic aplastic anemia failed to respond to this treatment, and they added the term refractory anemias to apply to these instances. Thus, from Ehrlich to Rhoads, the correct term for this disease probably is primary idiopathic refractory aplastic anemia, with hypoplasia of the bone marrow.

CLASSIFICATION OF OTHER TYPES OF APLASTIC ANEMIA

1. *Symptomatic or Secondary Aplastic Anemia.*—In contrast to the unknown etiologic basis for primary idiopathic aplastic anemia, a group of cases of known cause with similar symptoms, laboratory findings and pathologic manifestations has been described.

Among the various causative agents may be exogenous or endogenous toxins, such as benzene or its derivatives, arsphenamine, mustard gas (dichlorethyl sulfide), particularly the nitrogen mustards, nirvanol (phenylethylhydantoin), cinchophen, some sulfonamide compounds, particularly sulfanilamide, and trinitrotoluene. Roentgen rays, radium and radioactive materials may cause this type of secondary

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From the Sarah Morris Hospital for Children, Michael Reese Hospital, and the Department of Pediatrics, Northwestern University Medical School.

1. Ehrlich, P.: Ueber einen Fall von Anämie mit Bemerkungen über regenerative Veränderungen des Knochenmarks, Charité-Ann. **13**:300, 1888.

2. Frank, E.: Aleukia Hæmorrhagica, Berl. klin. Wchnschr. **52**:961, 1915.

3. Rhoads, C. P., and Miller, D. K.: Histology of the Bone Marrow in Aplastic Anemia, Arch. Path. **26**:648 (Sept.) 1938.

aplastic anemia. Radioactive phosphorus and the products of atomic fusion are other known causes. The toxins from sepsis, particularly those of staphylococcic, brucellosis and Salmonella choleraesuis infections and those from severe nutritional deficiencies, are causative agents. Metastatic tumors, such as neuroblastoma and sarcoma, and primary tumors, such as leukemia, by nature of their encroachment on the marrow tissue are other causes of this condition.

Stransky and Quintos [4] recently reported a severe irreversible aplastic anemia which sometimes occurs in hookworm disease. They were of the opinion that this anemia is due to exhaustion of the bone marrow following continued loss of blood, in addition to other factors, including dietary deficiency.

2. *Congenital Hypoplastic Anemia.*—Conditions under this classification, as the term denotes, are present from birth, and the aplasia tends to be confined to erythropoiesis, or a failure of red cell production, without the corresponding depression of leukocytes and platelets. This condition was probably first described by Finkelstein [5] in 1911, who noted anemia in infants without other signs of constitutional degeneration.

Josephs [6] in 1936 reported on 2 infants with this congenital type of anemia in whom the condition developed in the newborn period. Diamond and Blackfan [7] in 1938 described 4 cases under the title hypoplastic anemia, and other cases have been reported as congenital hypoplastic, idiopathic and hypoplastic congenital anemia.[8]

Since this is a congenital disease which makes its appearance in the newborn period or early infancy and affects chiefly only red cell production, it should easily be differentiated both clinically and in the literature from the condition under discussion.

3. *Refractory Anemia.*—Rhoads,[9] in 1938, in discussing primary or idiopathic aplastic anemia, introduced the term refractory anemia. In studying the bone marrow in his cases, he noted the following histologic types of refractory anemia: (1) that with hypocellular

4. Stransky, E., and Quintos, F. N.: On Hookworm Anemia (Aplastic Anemia in Hookworm Disease), Blood **2**:63, 1947.

5. Finkelstein, H.: Ueber die Anämien des frühesten Kindesalters, Berl. klin. Wchnschr. **48**:1829, 1911.

6. Josephs, H. W.: Anaemia of Infancy and Early Childhood, Medicine **15**:307, 1936.

7. Diamond, L. K., and Blackfan, K. D.: Hypoplastic Anemia, Am. J. Dis. Child. **56**:464 (Aug.) 1938.

8. Kohlbry, C. O.: Congenital Hypoplastic Anemia, J. Pediat. **19**:662, 1941. Rinvik, R.: Two Cases of Idiopathic Hypoplastic Anemia in Infants, Acta pædiat. **28**:304, 1941. Rubell, I.: Hypoplastic Congenital Anemia, J. Pediat. **20**:756, 1942. Esser, M.: Ueber kongenital-aplastische Anämie Typus Benjamin, Ann. pædiat. **154**:305, 1940. Høyer, K.: Aregenerative, Probably Congenital Anemia in Infant with Deficiency of Erythroblasts in Bone Marrow, Nord. Med. (Hospitalstid.) **14**:1097, 1942. von Sydow, G.: Hypoplastic Anaemia, Acta pædiat. **30**:365, 1943.

9. Rhoads, C. P.: Aplastic Anemia, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p. 33.

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marrow, or aplastic anemia; (2) that with immature cellular marrow; (3) that with active cellular marrow; (4) that with sclerosis of the marrow, and (5) that with megakaryocytic marrow. Our case falls under the first category of this classification.

4. *Primary Splenic Panhematopenia.*—This condition, recently described by Doan and Wright,[10] may be acute or chronic and involves the suppression of all blood elements, hematologically and clinically simulating aplastic anemia in that the numbers of red and white blood cells and platelets in the circulating blood are decidedly reduced. However, in contrast to the hypocellular bone marrow in primary and secondary aplastic anemia, the marrow in primary splenic panhematopenia is hyperplastic in relation to all elements. Doan subdivided this group into the congenital and the acute splenic types of panhematopenia. In all these cases there is an apparently normally functioning bone marrow with an abnormally functioning spleen. The normal spleen is one in which blood cell formation, blood cell sequestration and blood cell destruction are in physiologic balance. Theoretically, there is a possibility that certain hormones which affect the bone marrow, may arise or be secreted or excreted by the spleen.

According to the theory, these hormones may inhibit the normal function of the bone marrow. Doan suggested that the spleen may have an inherent capacity for unusual sequestration and destruction of the formed elements of the blood, which is particularly evidenced in any condition which causes the spleen to enlarge. When this unusual sequestration and blood destruction are manifested by the spleen, the bone marrow, in spite of hyperactivity, cannot compensate and, therefore, anemia, leukopenia and thrombopenia may result. Removal of the spleen, even though the underlying condition may be eventually fatal, may cause sufficient clinical improvement and prolongation of life to be a rational and worth while procedure.

This panhematopenia of Doan falls into the third category of the histologic types of refractory anemia as outlined by Rhoads, namely, refractory anemia, with active cellular marrow.

5. *Constitutional Infantile Anemia Resembling Pernicious Anemia (Fanconi's Disease).*—In 1927, Fanconi[11] described a fatal familial type of anemia in three brothers, 5, 6 and 7 years of age, with leukopenia, thrombopenia and hemorrhagic diathesis. The anemia was of the hyperchromic type with the predominant red cells megalocytic in type. Associated with this peculiar anemia were other congenital anomalies, such as microcephalia, strabismus and hypogenitalia. The bone marrow was hypoplastic. Other cases have been reported, of

10. (*a*) Doan, C. A.: Primary Splenic Panhematopenia, J. Lab. & Clin. Med. **30**:385, 1945. (*b*) Doan, C. A., and Wright, C. S.: Primary Congenital and Secondary Acquired Splenic Panhematopenia, Blood **1**:10, 1946.

11. Fanconi, G.: Familiäre infantile perniziosaartige Anämie (perniziöses Blutbild und Konstitution), Jahrb. f. Kinderh. **117**:257, 1927.

both familial and sporadic types.[12] None of these cases has shown aplasia of the bone marrow—at most hypoplasia. Because of the occurrence of the anemia in young life, it has been suggested that the condition is due to a fundamental inability of the marrow to produce cells. The familial character certainly suggests some congenital inherited defect of the bone marrow.

6. *Familial Hypoplastic Anemia of Childhood.*—Estren and Dameshek in 1947,[13] reported 8 cases of familial anemia in two families without other developmental anomalies. The authors noted that the cases reported by them were closest to the Fanconi type of familial anemia. While this group of rare cases showed hypoplasia of the bone marrow and pancytopenia, the disorder should offer no differential diagnostic difficulties with cases of primary idiopathic aplastic anemia.

REPORT OF CASE

Past History.—This female Negro child was delivered prematurely at seven months gestation and weighed 3 pounds (1,361 Gm.) at birth. Development and growth were normal. She received immunizations against smallpox, whooping cough and diphtheria. She contracted whooping cough at 2 years and measles and pneumonia at 6 years of age.

Family History.—The mother and father were living and well. The mother stated that she required blood transfusions at each delivery. The father had had "bad blood" and ulcers. There were five siblings, living and well.

Present Illness.—This girl was first seen at the age of 6 years, on July 26, 1942, complaining of pain in both ears. She dated this to a blow on the left side of her neck the previous day. At this time both ear drum membranes were thickened and discharged thick yellow material. Her tonsils were red and enlarged, and a round soft mass was palpable in the left side of the neck. Large posterior cervical glands were present bilaterally. The liver and spleen were not palpable. The red blood cell count on this admission was 3,990,000, with 72 per cent hemoglobin. The white blood cell count varied from 4,250 to 3,200, with 39 to 50 per cent filamented polymorphonuclear cells. She was followed in the dispensary. She was readmitted for tonsillectomy on Oct. 15.

The patient was again hospitalized from Jan. 1 to 31, 1947, because of anorexia, loss of weight, weakness of three months' duration, nocturnal fever and night

12. Émile-Weil, P.: Myélose aplasique infantile familiale avec malformations et troubles endocriniens: Contribution à l'étude du syndrome de Fanconi, Sang **12**:369, 1948. Hjorth, P.: Two Cases of Constitutional Anemia in Children, Nord. med. (Hospitalstid.) **7**:1313, 1940. Dacie, J. V., and Gilpin, A.: Refractory Anaemia (Fanconi Type): Its Incidence in Three Members of One Family, with in One Case a Relationship to Chronic Haemolytic Anaemia with Nocturnal Haemoglobinuria (Marchiafava-Micheli Disease or "Nocturnal Haemoglobinuria"), Arch. Dis. Childhood **19**:155, 1944. Uehlinger, E.: Constitutionelle infantile (perniciosaartige) Anämie, Klin. Wchnschr. **8**:1501, 1929. van Leeuwen, H. C.: Ein Fall von "konstitutioneller infantiler perniziosaähnlicher Anämie" (Fanconi), Folia haemat. **49**:434, 1933. Estren, S.; Suess, J. F., and Dameshek, W.: Congenital Hypoplastic Anemia Associated with Multiple Developmental Defects (Fanconi Syndrome), Blood **2**:85, 1947.

13. Estren, S., and Dameshek, W.: Familial Hypoplastic Anemia of Childhood, Am. J. Dis. Child. **73**:671 (June) 1947.

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sweats for three weeks prior to her admission. A rash developed over parts of the body for two weeks preceding admission. At that time she appeared chronically ill and showed extreme pallor of the nail beds and mucous membranes. The red blood cell count at the time was 1,220,000, with 6 Gm. of hemoglobin. The spleen was palpable 3 cm. below the costal margin, but the liver was not palpable. Both fundi contained numerous flame-shaped hemorrhages with surrounding exudate in the retina.

On January 10, a sternal puncture (Dr. Karl Singer) was followed by considerable oozing. Only a small amount of marrow could be aspirated. No resistance was felt when entering the marrow cavity; however, it was difficult to dislodge the cells. The smear showed a shift to the left of the erythroid series; many immature nonhemoglobinized erythroblasts were present. The white cell series showed only myeloblasts, premyelocytes and myelocytes. No mature white cells could be seen. The bone marrow pattern was that of hypoplasia with a shift to the left and arrest of maturation.

A biopsy of a persistently enlarged posterior cervical lymph node was done January 27. The pathologic report was "reticulum cell hyperplasia with moderate deposition of lipids." The child was given repeated transfusions and was discharged from the hospital on January 31, much improved. She was readmitted on February 5, because of abdominal cramps, weakness and headache. The hemorrhages in the retina persisted. On February 15, a lumbar puncture was done because of papilledema. The spinal fluid was normal. On March 14, the administration of folic acid was started. She was given 20 mg. twice the first day and 50 mg. twice a day for ten days thereafter, with thyroid, 1 grain (0.06 Gm.), twice a day for fifteen days, because of a basal metabolic rate of —16; but these had little effect on the red blood cell count, which remained at about 3,610,000, with 10 Gm. of hemoglobin. Aspiration of sternal marrow and sternal biopsy were attempted, but no marrow was obtainable.

At this point the parents were again interviewed, and a search was made of the past history for any ingestion or exposure to benzene, arsenic or radioactive substances as an etiologic factor; none could be elicited from the history, and neither the parents nor the five siblings showed any such anemia. On March 29, the child had a continuous epistaxis which packing did not completely control. Blood transfusion was necessary at this point. Besides the epistaxis there were bleeding of the gums and some purpuric phenomena noted. On April 3, a biopsy of bone marrow was undertaken with the patient under local anesthesia. Because of severe aplasia not enough marrow was yielded for study. Since frequent transfusions were necessary and since it was felt that the spleen might be either sequestering red cells or destroying them more rapidly than they could be formed, or inhibiting the bone marrow, splenectomy was decided on.

An epinephrine test done on May 7 showed the spleen to have little storage function for red blood corpuscles. Splenectomy was performed on May 16, at which time the red blood cell count after many transfusions was 4,010,000; hemoglobin measured 12 Gm., with 44,000 platelets. The pathologic report on examination of the spleen was "hyperemia with acute follicular hyperplasia and erythrophagocytosis." The spleen weighed 250 Gm. No significant rise in platelet count occurred after operation, and the postoperative course was uneventful.

The patient was discharged from the hospital May 29, on the thirteenth postoperative day, with a red blood cell count of 4,100,000, a white cell count of 6,100 and 41,000 platelets. She was quite active and in excellent spirits, and the appetite was good. She was followed in the outpatient department and had gained

4 pounds (1.8 Kg.) by the end of June after being home for one month. By the middle of July she had gained 2 more pounds (0.9 Kg.) but her red blood cell count had dropped to 1,800,000. She was readmitted for a transfusion and discharged after six days with a count of 3,000,000. Toward the end of July, she began to have some bleeding from her gums and mucous membranes and was readmitted for three weeks and given four transfusions. She was discharged on August 14, with a red blood cell count of 3,800,000. In October her weight had increased to 86 pounds (39 Kg.), 11 pounds (5 Kg.) more than at the time of her discharge in June. She continued to do fairly well at home until November 6, when she was admitted to the hospital for her final illness, because of fatigue, low blood count and overgrowth of granulation tissue in a previous biopsy wound of her right leg. On physical examination she appeared chronically ill. No

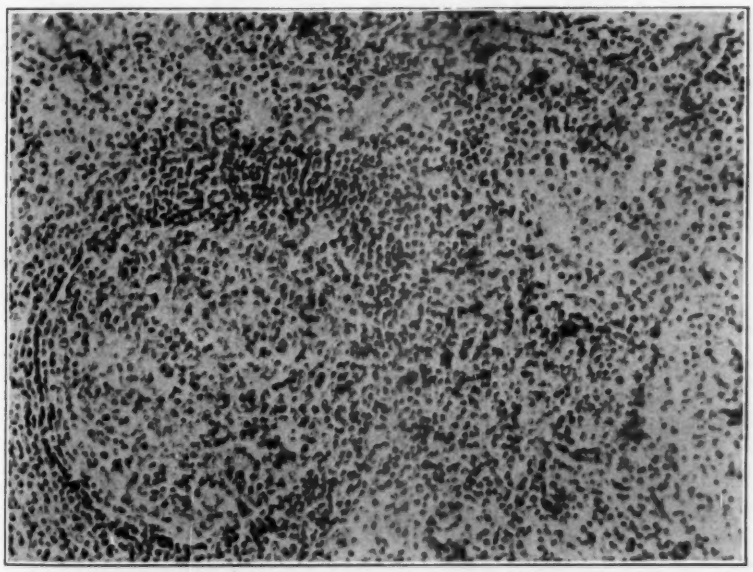

Fig. 1.—Low power view of section of spleen removed six months prior to death, showing follicular hyperplasia and a perifollicular zone of reticulum cells. No extramedullary hematopoietic foci are present.

significant lymphadenopathy was present. Some blood-tinged oozing appeared at the site of two previous biopsy scars which had ulcerated. During her stay in the hospital, frequent epistaxis occurred, which gradually became persistent and uncontrollable. On November 15, five days prior to death, a marrow specimen obtained from the iliac crest showed normal composition, except for diminution of megakaryocytes. The course of the patient's illness was progressively downhill, and she died on December 1.

Autopsy Report (Dr. Otto Saphir).—External Examination: The body was that of a well developed, fairly well nourished Negro girl appearing approximately 11 years of age. The body was 4 feet 11 inches (150 cm.) tall and weighed 65 pounds (29.5 Kg.). Both pupils were dilated but equal. The conjunctivas were extremely pale. The nose and mouth revealed numerous petechial hemorrhages over their surfaces. The nose in particular was crusted on its inside with clotted

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Chronologic Tabulation of Blood Findings, Laboratory Data and Therapy Used in Case of Primary Idiopathic Aplastic Anemia

Date	Red Blood Cells, Millions	White Blood Cells	Polymorphonuclear Forms	Lymphocytes	Eosinophils	Mononuclear Cells	Platelets	Transfusions, Cc. of Whole Blood	Therapy and Results of Tests
7/27/42	3.85	3,200	39	48	3	10	.....	.....	Wassermann and [illegible] reactions negative
7/30/42	3.99	4,250	50	44	..	6	.....	.....	
10/ 7/42	4.05	6,000	43	47	1	9	.....	.....	Clotting time: 5 [illegible]
									Bleeding time: ¾ [illegible]
1/ 2/47	1.22	1,900	35	56	1	8	.....	(1) 300	
1/ 6/47	1.68	2,500	18	79	1	2	Decreased low (hematocrit 13%)	.....	Negative reaction [illegible] sickling test
1/ 9/47	....	.....	..	..	..	..			Clotting time: 2 [illegible] 35 sec.
									Bleeding time: 15 [illegible]
1/11/47	1.42	3,150	31	62	..	7	.....	.....	
1/14/47	1.08	.....	..	..	..	..	100,000	.....	
1/18/47	1.73	2,650	..	..	..	..	.....	(2) 250	
1/23/47	2.32	.....	..	..	..	..	.....	(3) 250	
2/ 5/47	1.35	.....	..	..	..	..	.....	(4) 300	
2/ 6/47	2.08	1,900	40	44	1	15	.....	(5) 500	
2/ 7/47	2.23	.....	..	..	..	..	.....	.....	
2/11/47	3.7	.....	..	..	..	..	.....	(6) 500	
2/18/47	3.0	3,550	..	..	..	..	.....	.....	
2/19/47	2.84	3,450	36	48	..	16	.....	.....	
2/20/47	3.6	.....	..	..	..	..	.....	.....	
2/25/47	3.61	.....	..	..	..	..	.....	.....	
3/ 4/47	2.41	1,300	..	..	..	..	.....	.....	
3/11/47	2.56	2,500	18	77	..	5	.....	.....	Basal metabolic [illegible]
3/12/47	2.17	.....	..	..	..	..	.....	.....	Start folic acid, [illegible] b. i. d.
3/13/47	2.17	.....	..	..	..	..	.....	.....	Increase folic acid [illegible] 100 mg.
									1 gr. thyroid b. i. [illegible]
3/15/47	2.5	.....	..	..	..	..	.....	(7) 250	
3/21/47	1.2	.....	..	..	..	..	.....	.....	
3/28/47	1.1	1,100	..	..	..	..	.....	(8) 500	
3/29/47	2.30	.....	..	..	..	..	.....	(9) 500	
3/30/47	....	.....	..	..	..	..	.....	.....	Thyroid stopped
4/ 1/47	2.8	.....	..	..	..	..	.....	.....	
4/ 4/47	2.6	.....	..	..	..	..	.....	(10) 500	
4/ 5/47	3.1	.....	..	..	..	..	.....	.....	
4/15/47	1.9	2,400	11	82	6	7	.....	.....	Folic acid stopped
4/17/47	1.190	2,650	..	..	..	..	104,000	(11) 500	
4/21/47	2.42	.....	..	..	..	..	.....	(12) 500	
4/22/47	2.42	.....	..	..	..	..	.....	(13) 500	
4/25/47	2.5	.....	..	..	..	..	.....	(14) 500	
4/30/47	3.28	2,850	..	..	..	..	.....	.....	
5/ 6/47	1.56	2,956	..	..	..	..	.....	.....	
5/ 7/47	....	.....	..	..	..	..	.....	(15) 500	
5/10/47	....	.....	..	..	..	..	.....	(16) 500	
5/12/47	3.2	3,150	..	..	..	..	.....	(17) 500	
5/14/47	....	.....	..	..	..	..	.....	(18) 500	
5/15/47	....	.....	..	..	..	..	.....	(19) 500	
6/16/47	4.01	2,750	..	..	..	..	44,110	(20)1,000	
5/17/47	4.20	2,250	..	..	..	..	88,220	.....	Splenectomy
5/19/47	4.03	4,550	..	..	..	..	20,150	.....	
5/21/47	4.04	.....	..	..	..	..	40,000	.....	
5/27/47	4.11	6,100	26	65	3	6	41,000	.....	
6/ 6/47	3.81	4,700	33	53	..	14	22,800	.....	
6/12/47	3.22	3,500	..	..	..	..	41,860	.....	
6/27/47	2.10	7,600	5	89	..	6	16,800	.....	
7/11/47	1.81	4,200	11	86	..	3	.....	.....	
7/14/47	1.43	3,450	20	67	..	13	.....	.....	
7/15/47	1.35	.....	..	..	..	..	.....	(1) 500	
7/16/47	2.54	.....	..	..	..	..	.....	(2) 500	
7/17/47	3.05	.....	..	..	..	..	.....	.....	
8/25/47	1.84	5,400	17	75	..	8	18,400	.....	
9/ 2/47	1.67	.....	..	..	..	..	.....	(3) 500	
9/ 8/47	2.17	6,000	..	..	..	..	.....	.....	
9/ 4/47	....	.....	..	..	..	..	.....	(4) 500	
9/ 5/47	2.23	.....	..	..	..	..	.....	.....	
9/ 6/47	....	.....	..	..	..	..	.....	(5) 500	
9/ 8/47	2.76	.....	..	..	..	..	.....	.....	
9/10/47	....	.....	..	..	..	..	.....	(6) 500	
9/11/47	3.82	.....	..	..	..	..	.....	.....	
11/ 7/47	1.52	5,100	31	66	..	3	.....	.....	
11/10/47	....	.....	..	..	..	..	.....	(7) 500	
11/12/47	2.22	4,250	43	54	..	3	39,960	.....	
11/15/47	....	.....	..	..	..	..	.....	(8) 500	
11/17/47	3.26	.....	..	..	..	..	.....	.....	
11/19/47	2.45	.....	..	..	..	..	.....	.....	
11/21/47	1.30	.....	..	..	..	..	.....	(9) 500	
11/23/47	....	.....	..	..	..	..	.....	(10) 500	
11/24/47	0.88	.....	..	..	..	..	.....	(11) 500	
11/25/47	3.03	.....	..	..	..	..	.....	.....	
11/26/47	2.48	.....	..	..	..	..	.....	.....	
11/28/47	0.98	.....	..	..	..	..	.....	(12)1,000	
11/29/47	2.05	6,100	48	47	1	4	.....	.....	

Total blood transfusions from splenectomy (5/16/47) to death (12/1/47).....	12 = 7,500 cc.
Previous transfusions.....	20 = 9,350 cc.
Grand total.....	32 = 16,850 cc.

blood. There was a healed, raised, pigmented vertical scar 3 cm. long over the manubrium of the sternum. Over the upper midportion of the abdomen was a similar vertical scar 16 cm. long, with a lateral right angle extension 10 cm. long toward the left flank. There were numerous petechiae over the body but particularly on the extremities. These did not exceed 4 mm. in diameter.

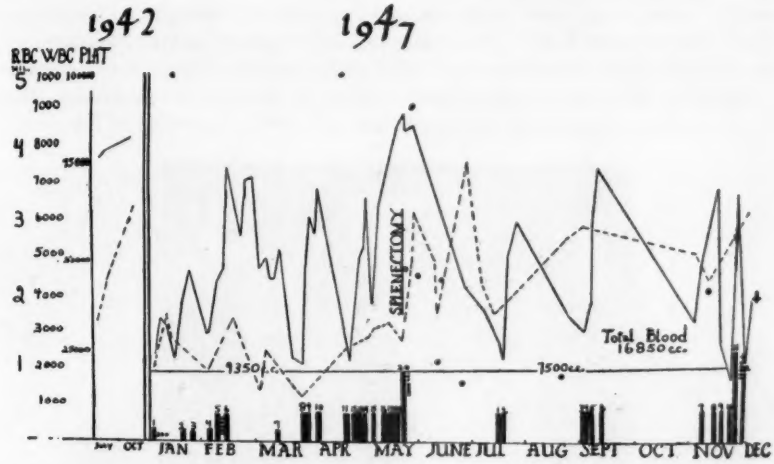

Fig. 2.—Chart showing results of blood counts and number and amount of blood transfusions during the course of illness in a girl with primary idiopathic aplastic anemia.

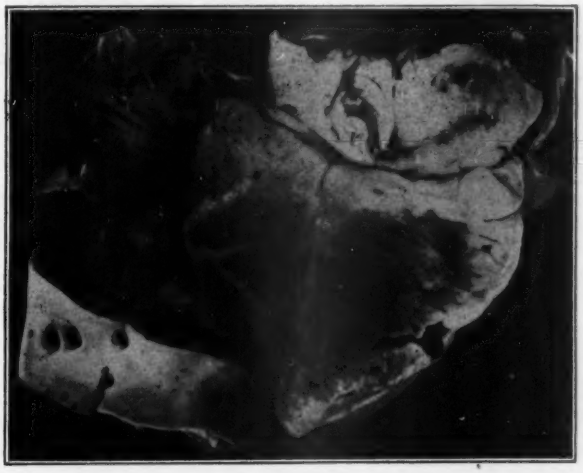

Fig. 3.—Gross section of the heart showing multiple petechiae.

Internal Examination: The midline fat measured 1 cm. in thickness. The peritoneal surfaces were smooth except in the left flank. The surfaces in this region were matted together with dense, fibrous, gray adhesions. The spleen could not be located. Petechial hemorrhages were evident over the peritoneum and intestine. The latter was distended and filled with dark fecal material. The

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pleural cavities revealed no changes. The thymus lay immediately over the anterior portion of the pericardium. It was yellow, soft and bilobular and measured 8 by 7 by 1 cm. The pericardial cavity contained no excess of fluid.

The heart weighed 150 Gm. The pericardial surfaces were smooth and glistening but covered with innumerable petechiae. These were particularly prominent over the visceral pericardium. The right ventricle measured 2.3 mm. at the pulmonary valve, 1 to 2 mm. at the tricuspid valve and 1 mm. at the lateral wall, while the left measured 8 mm. The tricuspid ring measured 6.2 cm., the pulmonary, 5 cm., the mitral, 6 cm. and the aortic, 5.2 cm. The valves were free of change. The subendocardium was discolored with many small petechial hemorrhages. None of these, however, appeared to be directly over or within the region of the bifurca-

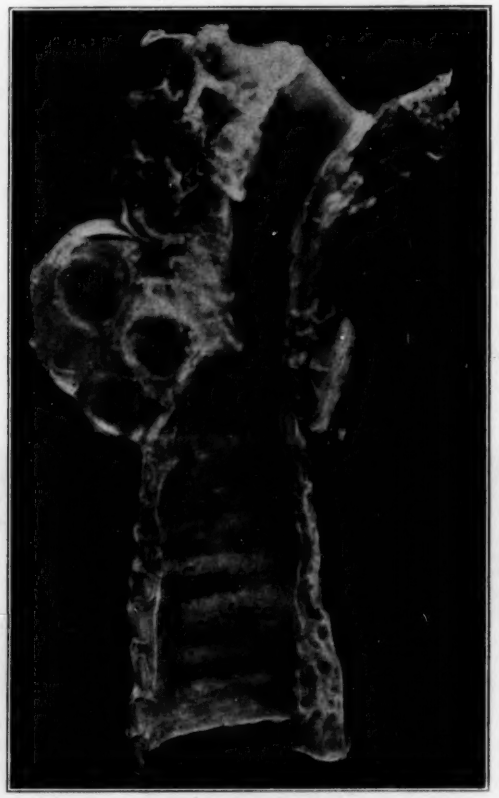

Fig. 4.—Gross section of trachea slit open to reveal compression by the enlarged tracheobronchial lymph nodes.

tion of the bundle of His. The myocardium as seen through the endocardium was mottled and had a tigered appearance. On section the tigering was still evident. The previously noted hemorrhages were present throughout the musculature. As a matter of fact, in portions of the right ventricle they occupied the entire thickness of the wall. The coronary artery and the great vessels arising from the heart revealed no changes.

The left lung weighed 210 Gm. and the right 185 Gm. There were numerous petechiae over the pleural surfaces throughout. The pleura over both lower lobes, particularly on the right, presented irregular patches of red or pink. The lung

underlying these zones felt more solid than that under the surrounding areas, which was feathery. On section, except for these red, more solid and granular zones, which exuded frothy fluid, the lungs were feathery, crepitant and gray. The tracheobronchial tree contained much frothy fluid. Alongside the right side of the trachea but not connected with its lumen was a lobulated gray structure filled with mucoid material and measuring 3 by 2 by 2 cm.

The liver weighed 1,325 Gm. Its surface was smooth and brown. On section the architecture was accentuated. The periportal zones were much larger than normal and gray but not confluent. The gallbladder and major bile ducts were free of change. The spleen was absent, and the previously noted gray, thick scar tissue was present at its site. The splenic artery was obliterated.

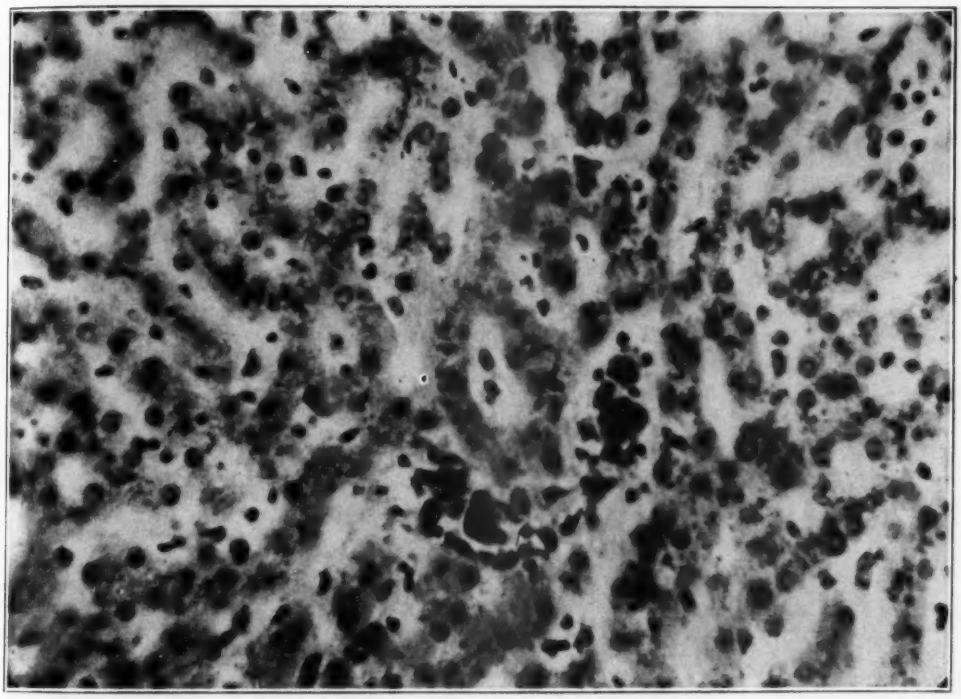

Fig. 5.—Low power photomicrograph of section of the liver showing hemosiderosis and fatty degeneration.

The kidneys together weighed 225 Gm. They were both larger and much paler than normal. On section the pallor was accentuated by the apparent lack of differentiation between the cortices and pyramids. The pelvis of the left was smooth and gray; that of the right, however, was thickened and purple. Its lumen was filled with dark, clotted blood. The ureters and urinary bladder were free of change.

The uterus was small and firm and showed no gross abnormality. Both ovaries revealed numerous simple cysts which did not exceed 5 mm. in diameter.

The adrenal glands were of normal size and position and showed no gross abnormality.

The pancreas showed no gross abnormality.

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The esophagus and stomach revealed multiple red submucosal hemorrhages, most pronounced in the region of the cardia. The rest of the gastrointestinal tract also showed multiple submucosal hemorrhages. The lumens of the terminal portion of the ileum and the colon were filled with tarry stool. The follicles in the same region were prominent.

The lymph nodes throughout the body, but particularly in the abdominal regions, were enlarged, soft and orange to deep red. In some areas, particularly along the splenic vein, they resembled accessory spleens.

Tests of the liver and lymph nodes, abdominal, as well as tracheal, showed them to be full of free iron.

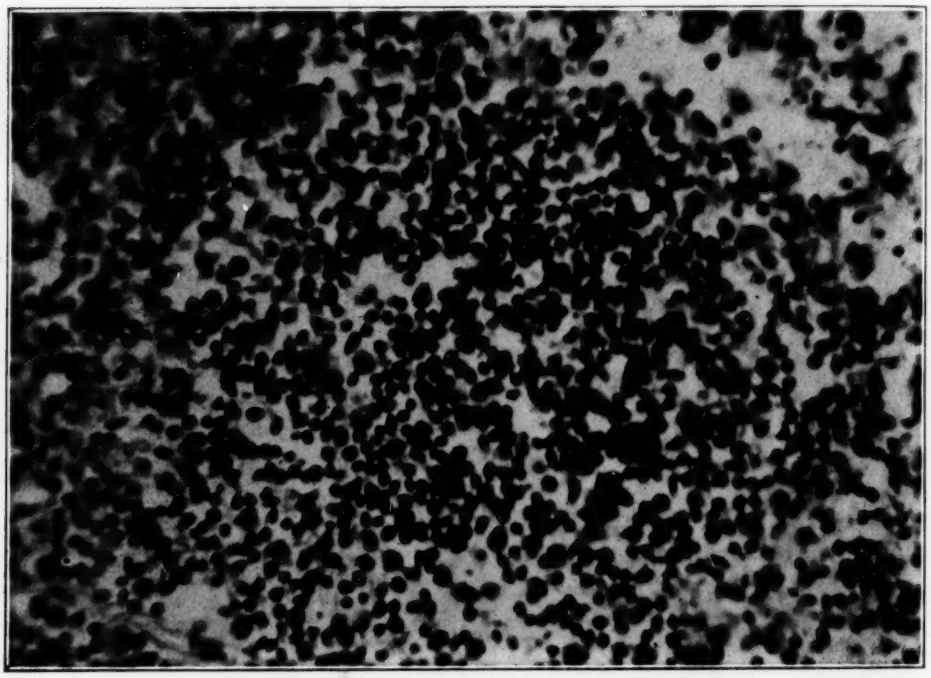

Fig. 6.—Low power view of section through a lymph node. Generalized hyperemia, with blood-filled sinusoids and phagocytes, is shown. Note resemblance to a hemolymph node.

The skeletal system revealed no change. However, no marrow could be expressed from the ribs or sternum. The marrow of the vertebrae, however, was much paler than normal.

Permission for examination of the brain could not be obtained.

Microscopic Description: Heart: Multiple small hemorrhages were present throughout in loose interstitial tissue and between muscle fibers.

Lungs: Small groups of alveoli were filled with erythrocytes. There was diffuse hyperemia of alveolar capillaries. Within some alveoli were foamy phagocytes, many with granular cytoplasm, others containing brown material. The parabronchial cyst was lined by columnar ciliated epithelium similar to that seen in the trachea.

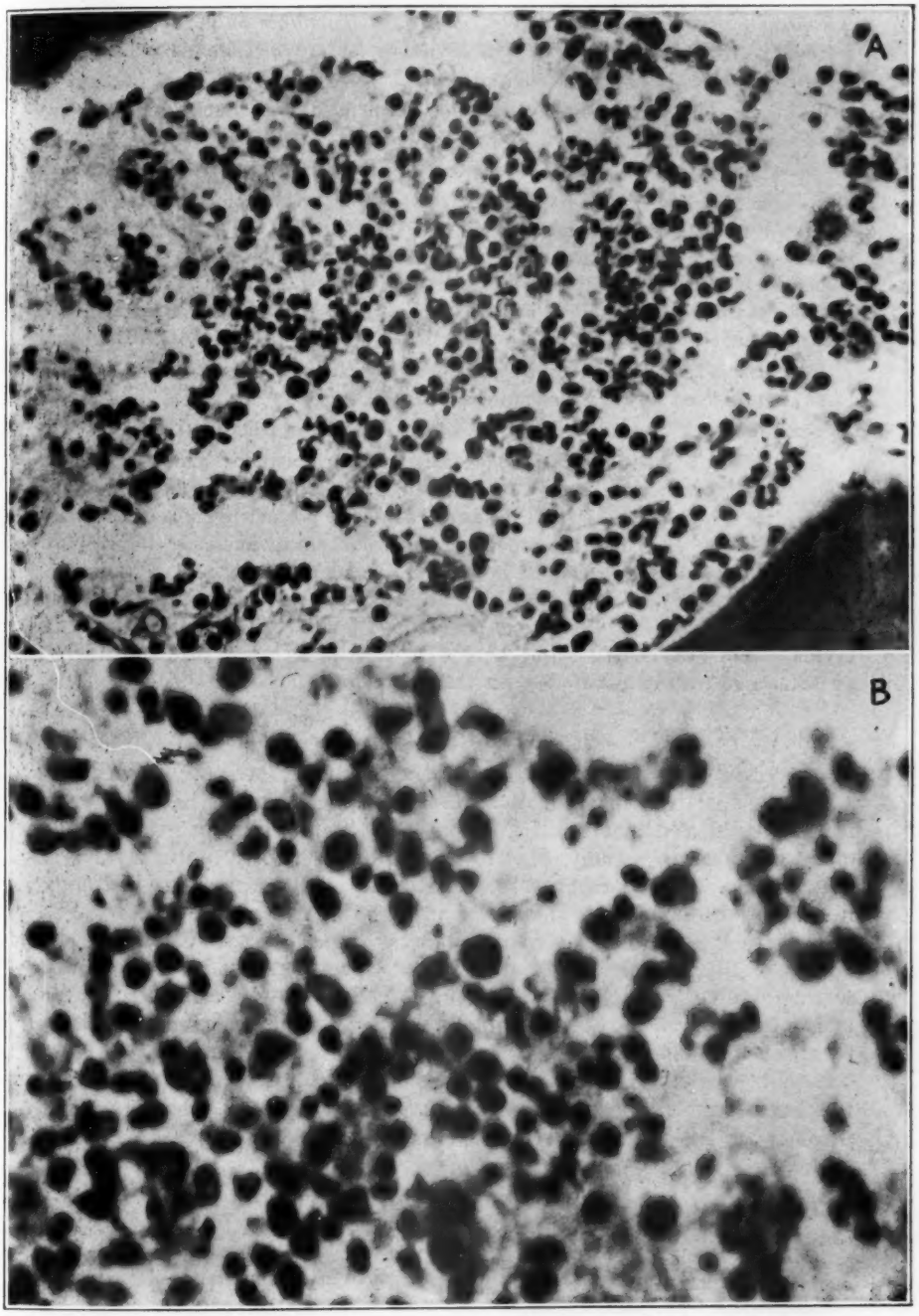

Fig. 7.—*A*, low power photomicrograph of section of bone marrow showing immature cells, lack of megakaryocytes and increase of fat cells. *B*, high power microscopic view of section of bone marrow.

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Liver: There was a great amount of brown pigment in granules within the cytoplasm of the liver and Kupffer cells. Accumulations of mononuclear cells resembling lymphocytes were present in periportal areas. Clumps of bile were noted in macrophages in the periportal zones.

Kidneys: There was cloudy swelling of tubular epithelium. Pink-staining granular material was present within many tubules.

No histopathologic changes were noted in the pancreas or adrenal glands.

Lymph Nodes: All the nodes appeared decidedly hyperemic. As a matter of fact, they resembled hemolymph nodes. All the sinusoids were filled with blood instead of with lymph. Within the follicles and about many of them were large mononuclear cells. Here there was a mixture of cellular elements as well, so that the picture was not unlike bone marrow. Many phagocytes contained golden brown granules.

Ovaries: There were several cysts lined by granulosa cells. The stroma was loose. It presented a typical immature appearance.

Gastrointestinal Tract: No changes were noted in the lymph follicles.

Bone Marrow: Different areas presented varying pictures. One observation, however, was constant: There was a definite paucity of megakaryocytes. Those which were seen were immature or abnormal. In some portions there was a scarcity of mature elements. Here, instead, were great numbers of immature forms, most of which appeared to be hemocytoblasts or very young erythrocytes. An increase of fat cells was noted in these zones, as well as a pronounced paucity of cells of the granulocytic series. Elsewhere, mature and young blast forms of both the erythroid and granulocytic series were seen. The picture was that of an arrest of maturation with extremely few intermediate forms.

PATHOLOGIC ASPECTS

According to Baar and Stransky,[14] the most striking observation at autopsy is that, in spite of severest anemia, there is no fatty infiltration of the red marrow. The marrow of the femur in growing and older children is usually described as sulfur yellow, more rarely, as rose yellow. If the marrow of the femur is intensely red, histologic investigation shows that this color is to be attributed to hemorrhages. However, the functioning hematopoietic bone marrow shows severe changes. In Engel's case,[15] pressure at several points caused a gray, watery exudate, in which no individual cells could be classified. Similarly, in rare cases of aplastic anemia in small children, the bone marrow is pale, gray or rose and lacking in cells. Nuclear red blood cells and myeloid elements are completely or almost completely absent; the occasional cells are almost always lymphocytes. However, an invasion of the fatty marrow by the red bone marrow also seems possible.[16]

14. Baar, H., and Stransky, E.: Die klinische Hämatologie des Kindesalters, Vienna, Franz Deuticke, 1928, pp. 137-138.

15. Engel, C. S.: Ueber einen Fall von perniciöser Anämie mit gelbem Knochenmark in den Epiphysen, Ztschr. f. klin. Med. **40**:17, 1900.

16. Kleinschmidt, H.: Aplastische (aregeneratorische) hämolytische Anämie im Kindesalter, Jahrb. f. Kinderh. **81**:1, 1915. Benecke, E.: Folia haemat. **21**:263, 1917.

In addition to the aforementioned pathoanatomic observations, hemosiderosis should be mentioned, a condition which is especially noteworthy when there is no urobilinogenuria.

In the case here reported it was noted at autopsy that the bone marrow was scant and considerably paler than normal. The hemosiderosis was prominent in the liver, and a prussian blue stain of hepatic tissue showed considerably more than normal iron pigment.

According to Whitby and Britton,[17] an extensive search will often reveal a few small islands of red marrow in some bone in the body. This was true on microscopic section through various bones in the case here reported; occasional areas of mature and young blast forms of the erythroid and granulocytic elements were noted. According to Whitby and Britton, the hemosiderosis is the result of large hemorrhages into the tissues and is occasionally produced by destruction of red cells that have been transfused.

Von Haam and Awny,[18] in reporting on the pathologic changes in spleens removed in Doan's clinic, noted that the spleen in cases of primary splenic panhematopenia was enlarged and that there was an increase in the size of the splenic pulp due to hyperplasia of the reticuloendothelial cells. Erythrophagocytosis and granulophagocytosis were observed, and the degree of hemosiderosis was increased in all cases. In three of the ten spleens examined by them in this condition, the lymphoid follicles were particularly enlarged. All showed a well developed perifollicular zone of reticulum cells.

The spleen removed in the case here reported weighed 250 Gm. and measured 15 by 9 by 3.5 cm. The surface was smooth and blue. On section the pulp was firm and blue-red, with prominent follicles. Hyperemia, with acute follicular hyperplasia and erythrophagocytosis, was noted on miscroscopic examination. There was also a perifollicular zone of reticulum cells, and no areas of extramedullary hematopoiesis were noted.

BLOOD PICTURE

The anemia in primary idiopathic aplastic anemia is usually severe, with erythrocyte counts below 2,500,000 and a correspondingly low hemoglobin concentration. The red blood cell count may drop below 1,000,000 per cubic millimeter. There is no great change in the size and shape of the cells, and no immature forms are seen. Reticulocytes are absent or only rarely seen. They may be counted up to 1 to 2 per cent but may be from the transfused blood.

Resistance in the fragility test is usually not increased; bleeding time is usually prolonged; clotting time and clot retractibility are normal. There are no signs of increased hemolysis; both the direct and indirect van den Bergh reactions are normal; there is no urobilinuria. The plasma is not yellow tinged and the stools reveal no increased pigment. The icterus index is not increased.

17. Whitby, L. E. H., and Britton, C. J. C.: Disorders of the Blood, ed. 5, Philadelphia, The Blakiston Company, 1946, pp. 780-781.

18. von Haam, E., and Awny, A. J.: Hypersplenism, Am. J. Clin. Path. **18**:313, 1948.

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The white blood cell count is low early in the disease. In the case here reported leukopenia was noted five years prior to the onset of severe anemia. Neutrophilic and eosinophilic polymorphonuclear forms are decreased, and a relative lymphocytosis exists. The white blood cell count may drop to 1,000 or under, with the lymphocytes forming from 70 to 80 per cent of the total; no abnormal white blood cells are seen.

Thrombopenia is the rule, and, when the platelet count drops below 40,000 to 60,000, purpura and bleeding from the mucous membranes may be expected.

BONE MARROW IN VIVO

It will be noted that the first bone marrow puncture in this case, on Jan. 10, 1947, showed hypoplasia with diminution of the megakaryocytes. This was repeated and, because insufficient marrow was obtained, a biopsy of bone marrow was performed on April 3, showing almost complete aplasia of the marrow. In contrast to these observations, a specimen of marrow obtained from the iliac crest five days prior to death showed almost normal composition with a diminished number of megakaryocytes. This agrees with the pathologic findings already mentioned, that at autopsy ". . . an extensive search will often reveal a few small islands of red marrow in some bone in the body."

The significance of these observations points to the necessity of obtaining marrow from different bones for evaluation, particularly in cases of aplastic anemia. Modern technics have been developed to facilitate obtaining marrow from the iliac crest, the spinous processes of the vertebrae and the tibia.

THERAPY

In a case of aplastic anemia of whatever category or classification, treatment of any type is at best ineffectual. Occasionally, without therapy, spontaneous and sustained remissions occur. Periodic blood transfusions are necessary to sustain life, and, as was noted in the cases reported by Josephs, death may follow the cessation of such transfusions. As stated by Rhoads, these cases are refractory to antianemia substances, such as liver in its various forms. According to Estren and Dameshek, daily injections of epinephrine, bone marrow transfusions and administration of bone marrow concentrate have all been unavailing in aplastic anemia.

In the case under discussion thyroid extract was given by mouth because of a — 16 basal metabolic rate, in the hope of stimulating the bone marrow.

Gendel [19] reported the use of folic acid as beneficial in the treatment of 3 cases of aplastic anemia. Folic acid was given to our patient in doses of 100 mg. by mouth for thirty days without significant improvement.

19. Gendel, B. R.: Folic Acid in the Treatment of Aplastic Anemia, J. Lab. & Clin. Med. **32**:139, 1947.

SPLENECTOMY

Whitby and Britton noted that in subacute and chronic cases of aplastic anemia removal of the spleen is a rational procedure in that the most accessible center for blood destruction, as well as the organ which is believed to control cell maturation, is eliminated. They stated:

> . . . We have now experience of six fully investigated cases in whom, after a long preliminary period of maintenance with transfusions, the spleen has been removed with an extremely successful result. We have also had complete failures, though none have been made worse.

Rhoads noted that transfusions have only a temporary effect. In the series reported by him, in 2 cases splenectomy was of benefit, in one case the remission lasting more than two years. In other instances splenectomy had no effect.

Blackfan and Diamond noted that splenectomy has been advised as a method of stimulating bone marrow production of erythrocytes, leukocytes and thrombocytes. Occasional instances of remission, either temporary or permanent, have been reported following this operation.

Frank and others considered that in cases of chronic aplastic anemia in adults, the spleen plays a decisive part in the pathogenesis, in that, according to some workers, it gives off substances into the blood which inhibit the activity of the bone marrow. He, therefore, considered, splenectomy as a rational therapy in this type of anemia. Estren and Dameshek noted that splenectomy has been performed in an occasional case of aplastic anemia both in adults and in children.

In cases of hypoplastic anemia, splenectomy with some beneficial results was reported by Diamond and Blackfan,[20] von Sydow and others. Estren and Dameshek reported cases of Fanconi's syndrome in which splenectomy was performed.

Estren, Suess and Dameshek reported a case of Fanconi's syndrome with splenectomy in which thrombopenic purpura and a bleeding diathesis were marked. They noted that

> . . . splenectomy was nevertheless undertaken because the patient was going rapidly downhill and it was felt the operation offered the only chance of improvement. The procedure was followed by a well defined reduction in the necessity for frequent transfusions, although the platelet level did not rise appreciably. The red cell and hemoglobin levels were well maintained and perhaps even favorably influenced.

Estren and Dameshek also reported pronounced improvement following splenectomy in one sibling in a family recently classified by them as having familial hypoplastic anemia of childhood. Finally, Doan and Wright [10b] noted in cases of primary splenic panhematopenia with hyperplastic marrow that removal of the spleen was curative. Doan [21] emphasized the intimate relationship of the spleen to the bone marrow and pointed out the depressive action which the

20. Blackfan, K. D., and Diamond, L. K.: Aplastic Anemia, in Atlas of Blood in Children, New York, Commonwealth Fund, 1944, p. 17.

21. Doan, C. A.: Pan-Marrow Hematopoiesis (L. Casei Factor) and Splenic Hematopenia: Experimental and Clinical Studies, Proc. Inst. Med. Chicago **16**:178, 1946.

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spleen may exert on the bone marrow in the various types of aplastic anemia.

TECHNIC BEFORE SPLENECTOMY

Prerequisite to splenectomy are frequent, daily if necessary, transfusions to bring the red blood cell count to as high a level as possible so that patient may withstand operation. The present patient was prepared by five daily transfusions, so that the red blood cell count rose from slightly above 1,000,000 to more than 4,000,000 on the day of operation.

Prior to operation, an epinephrine test was carefully performed. The technic of the epinephrine test, as described by Doan and Wright,[10a] is as follows:

> . . . During a fifteen to thirty minute base-line period, under basal metabolic conditions, the pulse, blood pressure, and two preliminary complete peripheral blood studies are obtained and the splenic outline is traced. Depending upon the age and vascular integrity of the patient, 0.5 to 1 cc. of 1:1,000 adrenalin chloride is injected subcutaneously. Blood studies are repeated at ten minute intervals until the pulse and blood pressure reach their maximum stimulation, which usually coincides with the greatest contraction of the spleen. The peripheral blood studies are then continued at fifteen minute intervals until the spleen has relaxed and the biphasic depression of the curve has been obtained.

Results of the epinephrine test made May 7 in the case here reported were as shown in the tabulation.

	Hemoglobin Concentration, Gm.	Red Blood Cells, Millions	White Blood Cells	Thrombocytes (Normal= 300,000 to 900,000)	Polymorphonuclear Forms	Nonsegmented Forms	Lymphocytes	Monocytes	Eosinophils	Basophils
Control 1	5.0	1.47	2,200	8,820	18	5	70	7	..	..
Control 2	5.0	1.58	3,200	9,780	35	4	48	12	..	..
Introduction of epinephrine										
15 min	5.0	1.95	6,400	12,950	20	2	70	6	..	..
30 min	5.0	1.81	3,550	5,430	20	2	74	4	..	..
45 min	4.7	1.96	3,350	9,800	17	8	68	6	..	..
60 min	4.5	1.87	2,500	11,220	33	10	49	7	..	..
1 hr. 15 min	5.0	1.71	2,000	10,260	24	15	57	4	..	..
1 hr. 30 min	4.5	1.46	2,050	5,840	34	16	43	7	..	..
1 hr. 45 min	4.3	1.41	2,100	.....	26	9	61	4	..	..

The results of the test, as noted, indicated that the spleen was not a source of extramedullary formation of blood cells, as no immature cells were thrown into the peripheral circulation following the administration of epinephrine. This was proved to be true in that the histologic examination of the spleen following its removal showed no extramedullary blood islands.

DIFFERENTIAL DIAGNOSIS

The differentiation of primary idiopathic aplastic anemia with hypocellular bone marrow from leukemia may be quite difficult or impossible clinically, with inclusion of examination of the peripheral

blood and even with sternal marrow puncture or biopsy of bone. I. A. Abt [22] reported the difficulty in distinguishing aplastic anemia from aleukemic leukemia in childhood.

I previously reported [23] on a patient who was observed for more than two years, with constant anemia, leukopenia, splenomegaly and a bleeding tendency. The condition for a long period was considered as a primary aplastic anemia, but on autopsy it proved to be chronic aleukemic myeloid leukemia.

Rhoads had the same personal experience in following cases for long periods in which refractory anemia was the only diagnosis possible by any clinical or histologic criteria and which developed evidence of leukemia as a preterminal feature. According to Rhoads,

> . . . The suggestion is strong that certain types of the anemia may well be considered to be preleukemic conditions. Unfortunately, many more examples will be required before this point can be established.

SUMMARY

The term aplastic anemia is no longer the simple one which Ehrlich originally proposed. It has been reclassified through the years and now includes the primary idiopathic type, the symptomatic or secondary type, the congenital hypoplastic type, the refractory anemia of Rhoads with five histologic subtypes, the primary splenic hematopenia of Doan and, finally, Fanconi's disease or constitutional infantile anemia resembling pernicious anemia and the familial hypoplastic anemia of childhood recently described by Estren and Dameshek.

This presentation deals only with primary idiopathic aplastic anemia, with a report of a case with splenectomy in an 11 year old Negro girl. The typical symptoms and signs of profound anemia, leukopenia, thrombopenia and hemorrhages into the skin, mucous membranes and retina were fully evidenced in this case.

All efforts were made to rule out a secondary cause, and no evidence of past infection or poisoning by any known secondary factor could be elicited. The parents, as well as five siblings, were all normal, and none exhibited an anemic tendency.

The child, of premature birth, first came under observation at the age of 6 years because of an accidental trauma. She was moderately anemic at this time and showed leukopenia, though she underwent tonsillectomy without hemorrhage or complications.

Five years later she again came under observation at the age of 11 years, at which time her red blood cell count was a little over 1,000,000. She was under close observation for eleven months, and for the first four and one-half months of this period she required increasingly frequent transfusions.

22. Abt, I. A.: Case of Aleukemic Leukemia with Clinical Symptoms of Plastic Anemia, M. Clin. North America **8**:427, 1924.

23. Abt, A. F.: Diagnosis of Leukemia in Childhood, M. Clin. North America **21**:89, 1937.

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During the course of her illness the liver, which was not at first palpable, enlarged, and the spleen was constantly enlarged and palpable.

At this point, it was impossible to differentiate the condition under observation from aleukemic leukemia, though biopsy of a cervical lymph node revealed no evidence of leukemia.

The technic of the epinephrine test is described. Results obtained in the case here reported are tabulated. This test indicated that no extramedullary hematopoiesis had been assumed by the spleen. The child stood the splenectomy well and made a rapid, uneventful recovery from the operation. Pathologic examination of the spleen corroborated the fact that no extramedullary hematopoiesis had been undertaken by this organ.

In the four and one-half months following splenectomy she gained 11 pounds, and her condition was satisfactory until six months after the operation, at which time rapid deterioration and death occurred.

A specimen of marrow obtained five days prior to death showed an almost normal composition with a diminished number of megakaryocytes.

A careful pathologic study revealed multiple hemorrhages throughout the body. Fatty degeneration of the liver with hemosiderosis was demonstrated. The bone marrow was rose-yellow and consisted histologically, for the main part, of immature cells, with a paucity or lack of megakaryocytes. These hypoplastic or aplastic observations in the bone marrow are the chief characteristic of the disease.

It has recently become evident, as this case so well demonstrates, that studies of marrow from various bones will aid in evaluation of the marrow function, particularly in aplastic anemia. Thus, in this case marrow from the iliac crest obtained five days prior to death showed a normal composition, while in a biopsy of marrow taken eight months previously, insufficient material was obtained for study. From the red blood cell level that this child was able to maintain without the aid of transfusions, we may speculate that approximately 20 per cent of her bone marrow was functioning normally. A marrow aspiration of a single bone which reveals insufficient marrow for study does not signify complete aplasia of the marrow of every bone in the body, as demonstrated in this case. Multiple bone marrow studies by newer technics would give a more adequate picture of the marrow function.

Sufficient authoritative evidence is presented to validate the theoretic and practical hypothesis which prompted splenectomy as a palliative therapeutic measure in this case. The immediate improvement following splenectomy and the amelioration of the child's general condition for six months following the operation seem to justify this therapeutic effort.

104 South Michigan Avenue (3).

DISCUSSION

DR. MILA I. PIERCE, Evanston, Ill.: We are indebted to Dr. Abt for reporting this unusual case of idiopathic aplastic anemia and for his review of the subject. Aplastic anemia of the idiopathic type is rare in children. I have seen only 2

cases similar to the one he described this morning. More commonly, aplastic anemia occurs as a secondary phenomenon to the noxious effect of a toxin or chemical which specifically damages the bone marrow. The idiopathic aplastic anemias recorded in the literature are often not clearly defined; when one adheres to the definition of a true aplastic anemia as a condition in which all the formed elements of the blood are depressed, one finds about 40 such cases on record. The aregenerative anemias, in which only the erythroid elements are depressed and the leukocytes and platelets are unaffected, are commoner.

There are several features of Dr. Abt's case which seem particularly significant to me. 1. The history suggests that the child's mother showed a bleeding tendency, with severe postpartum hemorrhages after each of five deliveries. It is likely, therefore, that she was also anemic. 2. The patient was born prematurely and may have been anemic in infancy owing to the combined factors of the anemia of the mother and her own prematurity. 3. At the age of 6 years, she was demonstrated to be anemic, and she showed an abnormal response to her infection (otitis media) in that she had leukopenia rather than leukocytosis. This may be interpreted as a suboptimum marrow response to an infection. 4. At the age of 11 years, the time at which the normal growth spurt makes additional demands on the marrow, she became more severely anemic and showed the pancytopenia. All this evidence suggests that familial and constitutional factors led to inadequate function of the bone marrow and to a true aplasia under conditions of stress.

The histologic changes in the bone marrow vary widely in different patients—from true aplasia and hypocellularity to hypercellularity. A common cell type which occurs in most instances is a small immature one designated the hematogone. Whether the variation in the marrow findings indicates a difference in the pathologic condition is questionable. At least, it is true that the same variation occurs in the secondary aplastic anemias. The bone marrow findings of these patients with aplastic anemia are remarkably similar to those of experimental animals treated with irradiation or nitrogen mustard. It is known that such agents are capable of producing irreversible changes.

Whether an unknown noxious agent is active in the conditions under discussion is not known. The role of the spleen in producing this type of idiopathic anemia is not understood. The indication for splenectomy is generally reserved for those patients who show a hypercellularity of the bone marrow, since this observation gives evidence of adequate marrow activity. The failure to obtain continued improvement in the case reported by Dr. Abt may be explained (possibly) by the effect of other reticuloendothelial tissues which developed a splenic-like function. Since there is no specific treatment for these patients, other than repeated transfusions, the role of the spleen needs to be more intensively studied.

Dr. John E. Cassidy, Washington, D. C.: Fortunately, one does not see the idiopathic form of aplastic anemia too frequently in children. When this diagnosis is made the outlook is grave. As was pointed out, the differential diagnosis is extremely difficult. One first must be certain that there is no known causative factor, such as poisons, exposure to radioactive substances or the presence of infection. Even when one has established that this "hypocythemia" is a primary affair, one is faced with differentiating it from the so-called aleukemic phase of leukemia. This picture in leukemia in children is a fairly common one. Bone marrow examination by means of sternal or tibial aspiration will help, but occasionally this can be confusing. Not all bone marrow in the body will show the same degree of activity or hypoactivity at the same time. The resemblance between these two conditions is striking at times, and the suggestion that idiopathic aplastic anemia be thought of as preleukemia is worthy of consideration.

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As Dr. Abt mentioned, splenectomy has been used before occasionally in the treatment of aplastic anemia, idiopathic type. The results were poor. Available evidence suggests that the spleen might be incriminated in this disease entity.

Splenic neutropenia, panhematopenia and thrombopenia have certain findings which are in common with aplastic anemia. There is a depression or aplasia of the various formed elements as indicated by their names. In idiopathic aplastic anemia and splenic panhematopenia, the peripheral blood pictures are identical but the marrow in the latter is normal or hyperplastic.

We are all aware of the favorable results reported in the use of splenectomy in the first three aforementioned conditions. It is logical to assume that, since there is such a close relationship between these and primary aplastic anemia, the procedure should be of some benefit in this condition.

It is interesting that histopathologic study of the spleen in the case presented showed perifollicular zones of reticulum cells. As Dr. Abt mentioned, this was a persistent observation in all forms of hypersplenism as reported by von Haan and Awny in spleens removed from more than 100 patients with essential hypersplenism. Thus, in this instance, there is a resemblance clinically and anatomically to conditions which are classified as hypersplenism and which have been benefited by splenectomy.

As we have been told, the improvement exhibited by this patient was definite but short lived. This indicates that there was some relation between the spleen and the depression of the formed elements, although this is not the complete answer by far.

The origin of primary aplastic anemia is still obscure, although there does seem to be a relation to a disturbance in splenic function in some cases.

HYPOCALCEMIA IN THE NEONATAL PERIOD

A Clinical Study

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AND
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CINCINNATI

THE STUDY to be reported arose as part of a general inquiry into the occurrence and significance of hypocalcemia in infancy and childhood. An earlier investigation [1] had indicated that a wide symptomatology, transcending by far the range of symptoms usually described for rachitic tetany, is associated with hypocalcemia in the postacidotic period of infantile diarrhea. It appeared of great interest to extend the inquiry to the problem of neonatal tetany.

Not until 1913 was the syndrome of neonatal tetany described by Kehrer, an obstetrician.[2] He reported 6 cases with spasms, accompanied by edema, vomiting or fever. Therapy with calcium chloride was dramatically effective. From the literature of the next two decades two reports, although not dealing with typical cases of neonatal tetany, should be mentioned because of their documentation by chemical data. Powers, in 1925,[3] described a case of persistent tetany in a 5 week old infant, with a calcium level of 5.9 and a phosphorus level of 8.9 mg. per hundred cubic centimeters of serum. A similar case of a 5 week old premature infant was reported in the next year by Griffith.[4] Shannon, in a series of papers,[5] refocused attention on tetany in newborn

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.

1. Rapoport, S.; Dodd, K.; Clark, M., and Syllm, I.: Postacidotic State of Infantile Diarrhea: Symptoms and Chemical Data, Am. J. Dis. Child. **73**:391 (April) 1947.

2. Kehrer, E.: Die geburtshilflich-gynäkologische Bedeutung der Tetanie, Arch. f. Gynäk. **99**:372, 1913.

3. Powers, G. F.: Tetany as a Cause of Convulsions in Very Young Infants, J. A. M. A. **84**:1907 (June 20) 1925.

4. Griffith, J. P. C.: Blood Calcium in Spasmophilia: Spasmophilic Manifestations in Infant of Five Weeks, J. A. M. A. **86**:828 (March 20) 1926.

5. Shannon, W. R.: Idiopathic or Hypoparathyroid Tetany in Children with Special Reference to Certain Psychic Manifestations, Arch. Pediat. **46**:346, 1929; Generalized Edema in Association with Tetany of the New-Born, ibid. **46**:549, 1929; The Relation of Minor Nervous Disturbances to Tetany in Children, ibid. **46**:679, 1929; Tetany, Generalized Edema and Cerebral Compression in the New-Born, ibid. **48**:153, 1931; Etiology of the Tetany Syndrome in the New-Born Infant, ibid. **51**:23, 1934; Cerebral Injury in the Newborn: Its Relation to Constitution and the Tetany Syndrome, Am. J. Dis. Child. **48**:517 (Sept.) 1934.

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infants. He redescribed the syndrome of Kehrer and stressed the combination of edema and cyanosis with convulsions. Unfortunately, he performed few calcium determinations. Another aspect of the symptomatology of neonatal tetany was brought forward by Bass and Karelitz,[6] who described 3 cases characterized by vomiting, fever and abdominal distention in the absence of spasms. The patients responded to calcium therapy; only one calcium determination was performed. Following these reports, the literature of the thirties is replete with accounts of individual cases or small groups of cases, showing convulsions or edema or vomiting as the cardinal symptom.[7] Of particular interest is a report by Willi[8] on a series of 13 well documented cases seen in one year at one hospital in Zurich, Switzerland.

Important studies dealing with the etiologic aspects of neonatal tetany were contributed by Bakwin,[9] who demonstrated that normal infants experience a fall of calcium and a rise of phosphorus in their serum in the first few days after birth, that in infants with tetany low calcium and high phosphorus levels and normal phosphatase activity are the rule and that administration of phosphate readily provokes tetany in newborn infants. He proposed the theory that transient hypoparathyroidism is a common occurrence in the newborn period. Infants with the tetanic syndrome represent the extreme beyond the normal variation.

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6. Bass, M. H., and Karelitz, S.: Tetany Accompanied by Hyperpyrexia and Vomiting in the First Days of Life: Unusual Syndrome, J. A. M. A. **97**:1372 (Nov. 7) 1931.

7. (*a*) Nesbit, H. T.: A Syndrome Occurring in the Neonatal Period Manifesting Tetany-Like Symptoms, Am. J. Dis. Child. **44**:287 (Aug.) 1932. (*b*) McGavran, E. G.: Spasmophilic Tetany in the New-Born, J. A. M. A. **99**:115 (July 9) 1932. (*c*) Drucker, P.: Aetiology of Convulsions in Early Infancy, Acta pædiat. **16**:572, 1933. (*d*) Guild, H. G.: Tetany of the Newborn, Internat. Clin. **3**:46, 1933. (*e*) Bloxsom, A., and Nicholas, H. O.: Tetany Calcipexicus of the Newborn Infant, South. M. J. **26**:883, 1933. (*f*) Small, A. S.: Tetany in Young Infants, J. Pediat. **2**:681, 1933. (*g*) Rothstein, J. L.: Low Calcium Tetany in the Newborn, ibid. **5**:341, 1934; (*h*) Unusual Case of Low Calcium Tetany Without Convulsions in a New-Born Infant, J. A. M. A. **105**:1189 (Oct. 12) 1935; (*i*) Low Calcium Tetany of the Newborn, J. Pediat. **6**:644, 1935. (*j*) Craig, J. D.: Tetany of the Newborn, ibid. **4**:219, 1934. (*k*) Greenwald, H. M., and Palinsky, M.: Tetany of the Newborn, Acta pædiat. **17**:386, 1935. (*l*) Starin, I.: Tetany in the Newborn, Arch. Pediat. **52**:489, 1935. (*m*) Snelling, C. E.: Tetany in the Newborn, J. Pediat. **7**:465, 1935. (*n*) Farr, L. E.: Tetany in the Newborn, Yale J. Biol. & Med. **9**:333, 1937. (*o*) Snelling, C. E., and Brown, A.: Tetany in the Newborn, J. Pediat. **10**:167, 1937. (*p*) Shannon, W. R.: Tetany Syndrome in New-Born Infants: Remote Deposit of Calcium Salts Following Injection of Sodium Gluconate, Am. J. Dis. Child. **56**:1046 (Nov.) 1938.

8. Willi, H.: Die Neugeborenenspasmophilie, Monatsschr. f. Kinderh. **80**:309, 1939.

9. Bakwin, H.: Pathogenesis of Tetany of the New-Born, Am. J. Dis. Child. **54**:1211 (Dec.) 1937; Tetany in Newborn Infants, J. Pediat. **14**:1, 1939.

In the last years few reports have appeared.[10] The question of a renal factor in the causation of the disease was raised by Snelling,[11] who reported 2 cases of tetany in infants with congenital renal anomalies but included also 9 other cases with moderate and transient elevations of the nonprotein nitrogen of the blood.

The impression clearly emerges that the syndrome of neonatal tetany, as described in the literature, differs in many respects from other forms of tetany. Chemically, it is characterized by a tendency to high phosphorus and low calcium values; clinically, carpopedal spasms and laryngeal stridor appear rarely, and convulsions, vomiting and edema commonly, as the chief manifestations. The symptomatology bears an obvious resemblance to that of the postacidotic state of infants. Dysfunction of the parathyroids, or perhaps of the kidneys, has been considered as an etiologic factor.

MATERIAL

The clinical material of the present report includes a group of 33 newborn infants with hypocalcemia and a variety of symptoms who were observed at the Children's Hospital, Cincinnati, from 1937 to 1947. Until 1944, only 5 instances of tetany of the newborn were recorded; with increased attention to the diagnosis, 12 instances of tetany were noted in 1946 and as many in 1947. Experience with the patients at the Children's Hospital stimulated a series of observations on newborn infants in the nursery of the Cincinnati General Hospital, with the purpose of defining normal levels of calcium, phosphorus and nonprotein nitrogen and of assessing the degree of association between certain clinical signs and the plasma level of calcium in a sampling of newborn infants. The infants studied were divided into 2 groups: (1) 48 infants who did not show any signs of tetany and (2) 24 full term infants who showed signs suggestive of tetany. An additional study was conducted on a group of 12 premature infants with symptoms of tetany. Finally, reference is made to 9 ill infants with hypocalcemia who were seen in the nursery for the newborn of the Cincinnati General Hospital during the period of study.

SERIES AT THE CHILDREN'S HOSPITAL

The 33 patients, data on whom is presented in table 1, embrace those infants seen at the Children's Hospital from 1937 through 1947. Few were admitted with the diagnosis of tetany. For the most part, they were vomiting or having convulsions. Several children who vomited persistently were suspected of having intestinal obstruction. In many children, convulsions were attributed to an intracranial birth injury. The patients who received no antitetanic therapy are listed first, followed by those who were treated. Each group is arranged in order of age at onset of symptoms.

10. Bloxsom, A.: Treatment of Tetany of Newborn Infant with Dihydrotachysterol, J. Pediat. **16**:344, 1940. Kendig, E. L.: Tetany in the Newborn Infant, ibid. **21**:510, 1942.

11. Snelling, C. E.: Disturbed Kidney Function in the Newborn Infant Associated with Decreased Calcium: Phosphorus Ratio, J. Pediat. **22**:559, 1943.

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TABLE 1.—*Symptoms, Course and Chemical Data of 33 Pat*

Case No.	Sex	Weight at Birth, Gm.	Age at Onset, Days	Birth History	Symptoms	Course in the Hospital
1	M	2,700	0	Normal	Vomiting of green material and abdominal distention since shortly after birth; at examination: lethargy and edema of legs	Abdominal distention persisten stool containing blood; sclered like consistency of skin; premor hematemesis
2	M	2,400	0	Delayed breathing	Scleredema; cyanosis; weak cry; tachycardia with loud systolic murmur	Died 12 hr. after admission to C dren's Hospital
3	F	4,100	0	Delayed breathing	Generalized tonic and clonic convulsions since shortly after birth; at times projectile vomiting; high pitched cry; at examination: inspiratory stridor and irregular respirations	Except for occasional twitchi and presence of Chvostek's s uneventful
4	M	2,600	0	Normal	Refusal to nurse and vomiting of coffee-ground material; vomiting of bright blood; meconium stool present	Laparotomy; no site of intesti obstruction found; placed on in venous drip; became severely ed atous; stools contained blood; d on fourth day
5	M	3,100	1	Severe labor; cyanotic at birth	Vomited blood on first day; vomiting persisted; on second day stiffening spells; stuporous; at examination: irritable but drowsy	Improved slowly, but continued regurgitate
6	M	3,000	1	Normal	Vomited large amount of bright red blood; continued to vomit but without blood	Continued to regurgitate but lesser degree
7	F	2,300	2	Normal	Possible erythroblastosis; at examination hyperirritable; facial edema; inspiratory stridor	Refused to feed and continued perirritable; tracheoesophageal tula found for which operation formed; did poorly and died shor afterward
8	M	3,800	4	Normal	Convulsions every 4 hours limited to face and left side of body; at examination, 2 convulsions	During 5 day stay in hospital tient continued to have convulsi
9	M	2,900	0	8 months' gestation; normal	Projectile vomiting since day of birth; hyperirritability; convulsions; conjugate deviations of eyes; at examinations: Chvostek's sign present; facial edema	Rapid improvement within one following antitetanic therapy
10	M	2,900	0	8 months' gestation; normal	Jaundice and anemia; edema and lethargy	Infant became more edematous, veloped high pitched cry; improv eventually
11	M	3,000	0	Delayed breathing	Repeated convulsions with cyanosis 12 hours after birth; on examination: heart rate 96 per min.; Chvostek's sign present	Except for some vomiting, uneve ful course
12	M	2,600	0	Difficult delivery; resuscitation required	Shaking and trembling of body; at examination Chvostek's sign positive, ankle clonus	Vomiting at first and hyperirr bility; improved on day after st of antitetanic therapy
13	F	3,400	0	8 months' gestation; cesarean section	At examination: cyanosis and edema	Convulsion 4 hr. after admissi regurgitation of feedings; hyp ritability, abdominal distenti vomiting of bile-stained mater blood in stools; after start of cium therapy loss of weight of 1 cessation of vomiting
14	M	2,500	0	Premature	Cyanosis and vomiting; at examination: irregular breathing	Steady improvement following th apy
15	M	4,200	1	Normal	Persistent vomiting, 1 convulsion; at examination: irritability; tremor of limbs, Chvostek's sign present	After 2 days of therapy no m convulsions, but continued p feeding
16	M	3,400	1	Normal	Convulsions 16 hours after birth; at examination: right-sided clonic movements of limbs, conjugate deviations of eyes	Two convulsions on first day in h pital; after calcium therapy no ther convulsions
17	F	4,000	1	Normal	Vomiting; at examination: stiffness, lethargy, irritability with tremors of extremities	After start of antitetanic thera cessation of vomiting, edema a lethargy
18	F	2,700	1	Normal	Edema of hands and feet; irritability, stiffness, vomiting and cyanosis; at examination: carpopedal spasm, Chvostek's sign present, systolic murmur	Improvement following calcium th apy
19	M	4,000	2	Normal	Vomiting of bloody material and blood in stools; at examination; drowsiness, coarse cry, hyperirritability and edema of face and extremities	Rapid improvement following a tetanic therapy

Comment	Antitetanic Therapy	Results of Laboratory Determinations: Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.	Phosphatase, Bodansky Units	Nonprotein Nitrogen, Mg./100 Cc.	Protein, Gm./100 Cc.	Other Results	Time of Sample Relative to Start of Therapy
ically, meconium ileus con-ered; roentgenographic amination negative	None	7.4	8.6	...	72	...	.....	Before
ropsy: cardiac dilatation, tent ductus arteriosus, con-tion of viscera; minimal ebellar, subarachnoid morrhage	None	7.2	8.0	...	68	...	Carbon dioxide, 23 mEq./L. Chloride, 102 mEq./L.	Before
.....	None	8.4	8.2	...	..	...	.....	Before
		9.1	7.7	6.3	..	...	.....	7 days no therapy
eated roentgenographic aminations showed iodized passing through gastro-eric tract, but possibility incomplete and intermittent struction considered	None	7.0	6.1	...	51	...	.....	Before
nal fluid: slightly yellow; otein, 108 mg./100 cc.	None	8.4	3.4	...	..	...	.....	Before
nal fluid: colorless, protein, mg./100 cc.; roentgeno-aphic study of gastro-teric tract negative	None	7.6	7.0	...	44	...	Carbon dioxide, 26 mEq./L.	Before
		9.9	8.4	...	48	...	Chloride, 97 mEq./L.	10 days no therapy
ropsy: diffuse pneumonia, ght subdural hemorrhage, oracotomy with end to end astomosis of esophagus	None	7.4	...	...	..	...	.....	Before
d erythroblastosis; spinal id: colorless, protein 86 mg./ cc.; subdural punctures uivocal	None	6.6	...	...	..	...	.....	Before
.....	Calcium chloride, 2 Gm. for 6 days	7.6	9.0	8.0	31	5.6	Chloride, 111 mEq./L.	Before
		10.0	7.1	...	..	...	.....	2 days after
ere erythroblastosis; later, ns of hepatic impairment; ental development satis-ctory?	Calcium chloride, 3 Gm. for 3 days; dihydrotachysterol, 2.5 mg. for 3 days	6.6	6.8	15.6	87	5.6	Bilirubin, 31 mg./100 cc.	Before
		11.4	3.7	12.7	38	...	Bilirubin, 23 mg./100 cc.	5 days after
sults of subdural puncture ormal	Calcium chloride, 3 Gm. for 2 days; calcium chloride, 2 Gm. for 2 days; dihydrotachysterol, 1.25 mg. for 5 days	7.2	...	...	..	...	.....	Before
		12.1	5.0	...	..	...	.....	4 days after
nal fluid: yellow; protein, mg./100 cc.	Calcium chloride, 1 Gm. for 6 days	7.0	5.4	...	42	4.3	.....	Before
		9.4	...	...	..	...	.....	4 days after
ther known diabetic; 2 pre-ous babies died soon after rth; roentgenographic exam-ation showed multiple di-ted loops of small bowel: econium ileus suspected	Calcium chloride, 1.5 Gm. for 4 days	7.4	7.8	...	35	3.7	Blood sugar, 61 mg./100 cc.	Before
		10.5	3.7	...	..	3.9	.....	3 days after
.....	Calcium chloride, 1 Gm. for 3 days	6.6	7.8	...	43	...	Chloride, 100 mEq./L.	Before
nal fluid: bloody but color-ss, after centrifugation; pro-in, 180 mg./100 cc.	Calcium chloride, 2 Gm. for 2 days	8.2	6.2	...	45	...	.....	Before
		10.8	...	...	..	...	.....	7 days after
.....	Calcium gluconate, 0.3 Gm. intravenously; calcium chloride, 2.5 Gm. for 4 days; calcium chloride, 1.25 Gm. for 6 days	8.5	6.1	...	..	...	.....	Before
		12.5	8.0	...	..	...	.....	7 days after
entgenographic examination gative except for delay in mptying of esophagus	Calcium chloride, 2 Gm. for 1 day; calcium chloride, 1 Gm. for 2 days	8.8	7.2	5.4	98	...	.....	Before
entgenographic examination cause of suspected tracheo-ophageal fistula, negative	Calcium chloride, 2 Gm. for 3 days	8.3	5.8	...	..	...	.....	Before
		11.0	5.4	...	..	...	.....	5 days after
o roentgenographic exam-ations of gastroenteric act, negative	Calcium chloride, 3 Gm. for 2 days; calcium chloride, 2 Gm. for 2 days; calcium gluconate, 4 Gm. for 3 days; dihydrotachysterol, 2.5 mg. for 3 days; dihydrotachysterol, 1.25 mg. for 4 days	8.4	6.0	...	32	4.1	Carbon dioxide, 25 mEq./L. Chloride, 111 mEq./L.	Before

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TABLE 1.—*Symptoms, Course and Chemical Data of 33 Patients*

Case No.	Sex	Weight at Birth, Gm.	Age at Onset, Days	Birth History	Symptoms	Course in the Hospital
20	M	4,400	3	Normal	Vomiting of bloody material, tarry stools; at examination: 1 generalized convulsion; edema, hoarse cry, ankle clonus	Continued vomiting throughout h pital stay; did well at home
21	F	4,500	3	Normal	Hoarse cry; generalized twitchings; cyanosis	Convulsions for 13 days in hosp while on intermittent calcium conate therapy; improved foll ing continuous parathyroid extr therapy
22	F	3,800	3	Normal	About 20 convulsions on third day; at examination: drowsy; rapid breathing	Drowsy most of the time; no ot symptoms
23	F	3,500	4	Normal	Frequent generalized convulsions; at examination: convulsions and conjugate deviations of eyes	One day after institution of tre ment convulsions stopped
24	F	4,300	5	Normal	Failed to nurse well; convulsions recurring every 2 to 3 hr.; at examination: almost constant twitchings, slight edema, respirations irregular, bradycardia (80 per min.), carpopedal spasm, Chvostek's sign and ankle clonus present	No immediate response to intra nous therapy with calcium glu nate but relaxation after seve hours; uneventful recovery
25	M	3,300	6	Normal	Convulsions	In first 24 hr. 2 convulsions, th started on calcium therapy w improvement
26	M	3,400	8	Normal	Frequent twitchings of face and extremities; vomiting; several convulsions; some laryngeal stridor; at examination: stiffness, slight edema, positive Chvostek's sign and slight tremors	Decided improvement after insti tion of antitetanic therapy
27	F	3,300	8	Normal	Repeated convulsions; at examination: 1 convulsion with conjugate deviation of eyes	Repeated convulsions while on phen barbital therapy; none after c cium therapy started
28	F	3,000	8	Normal	Choking and jerking when fed; later generalized convulsions occurring every ½ hr.; at examination: edema, Chvostek's sign and ankle clonus present	Several convulsions during first hr.; then uneventful recovery
29	F	2,900	9	Normal	Generalized convulsions	On therapy with sedatives convu sions continued, but ceased af institution of antitetanic thera
30	M	3,300	9	Normal	Convulsions of right arm and hand, becoming more frequent; at examination: 1 convulsion, conjugate deviations of eyes, inspiratory stridor, Chvostek's sign and ankle clonus present	While on therapy with calcium la tate somewhat drowsy and nursi poorly; improved on change to c cium chloride
31	M	3,600	11	Normal, by cesarean section	Repeated twitchings and edema of face and hands; at examination: carpopedal spasm, facial edema, systolic heart murmur, 1 convulsion	Within 1 day after start of calci therapy no more convulsions
32	M	3,000	11	Normal	Repeated twitchings; noisy respirations; horizontal nystagmus; at examination: ankle clonus, clonic movements of extremities, Chvostek's sign present	On second day after calcium thera decrease of tetanic manifestati
33	F	3,600	13	Normal	Fever, irritability; at examination: 3 convulsions, Chvostek's sign and ankle clonus present	Irritability and regurgitation disa peared promptly after calcium th apy started

Comment	Antitetanic Therapy	Results of Laboratory Determinations: Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.	Phosphatase, Bodansky Units	Nonprotein Nitrogen, Mg./100 Cc.	Protein, Gm./100 Cc.	Other Results	Time of Sample Relative to Start of Therapy
...al fluid: colorless, protein, ... mg./100 cc.; findings of 4 ...ntgenographic examinations: ...ardiospasm, 1 gastric hyper-...istalsis and pylorospasm, ...normal	Calcium gluconate, 1 Gm. for 2 days	8.8	5.5	...	32	4.5	Carbon dioxide, 29 mEq./L. Chloride, 100 mEq./L.	Before
...ody spinal fluid on 2 occa-...ns; traumatic punctures? ...age of 9 years, 1 convulsion ...llowing blow on head, an-...her later in sleep; epilepsy?	Calcium gluconate, 2 Gm. for 1 day; after 13th day in hospital, 100 units parathyroid extract and 4 Gm. of calcium gluconate, for 13 days	7.9 8.0 11.2	9.7 9.8 6.5	9.9	.. .. ..	... ...	....	Before 6 days no therapy 5 days after
.....	Calcium chloride, 2 Gm. for 2 days; calcium chloride, 1 Gm. for 3 days; dihydrotachysterol, 1.25 mg. for 5 days	6.4	5.0	11.6	..	5.3	.....	Before
...fourth day of life convul-...ns treated by 1 dose of cal-...m; asymptomatic until 11th ...y, when convulsions recurred	Calcium chloride, 2 Gm. for 3 days; calcium chloride, 1 Gm. for 10 days	7.7 10.2	... ...	... ...	.. ..	... ...	....	Before 2 days after
...al fluid: clear, protein, 100 ...g./100 cc.; had some cal-...m therapy before admission	Calcium chloride, 3 Gm. for 3 days; calcium lactate, 3 Gm. for 5 days; dihydrotachysterol, 2.5 mg. for 1 day; dihydrotachysterol, 1.25 mg. for 5 days	5.0 10.4	5.8 4.7	... 11.5	76 32	... ...	*p*H, 7.49 Carbon dioxide, 27 mEq./L.	Before 6 days after
...nal fluid: slightly yellow, ...otein, 49 mg./100 cc.; results ... subdural punctures normal	Calcium chloride, 2 Gm. for 3 days	6.4 9.8 11.4	9.6 5.9 3.8	5.6 4.2 3.8	29	5.9 5.5 ...	....	Before 2 days after 9 days after
...nal fluid: colorless	Calcium chloride, 2 Gm. for 1 day; calcium chloride, 1 Gm. for 2 days; dihydrotachysterol, 1.25 mg. for 3 days	6.8	9.2	6.0	37	4.9	.....	Before
.....	Calcium chloride, 1 Gm. for 3 days	7.5	...	...	..	...	.....	Before
...nal fluid colorless; protein, ... mg./100 cc.	Calcium chloride, 3 Gm. for 1 day; calcium chloride, 2 Gm. for 2 days; calcium chloride, 1 Gm. for 5 days	7.2 11.8	11.2 3.8	... 6.8	48 37	4.8 ...	....	Before 6 days after
.....	Calcium gluconate, 0.5 Gm. and 10 units parathyroid extract intravenously; calcium chloride, 3 Gm. for 3 days; calcium chloride, 1.5 Gm. for 3 days; dihydrotachysterol, 1.25 mg. for 3 days	7.2 7.2 11.5	... ...	... ...	.. .. ..	... ...	....	Before 3 days no therapy 1 day after
...nal fluid: clear, protein, 47 ...g. 100 cc.	Calcium gluconate, 2.5 Gm. for 1 day; calcium lactate, 5 Gm. for 5 days; parathyroid extract, 15 units; calcium chloride, 3 Gm. for 2 days; calcium chloride, 1.5 Gm. for 4 days	7.0 10.0 10.8	9.1 9.2 7.7	9.7 10.0 9.5	33	... ...	....	Before 3 days calcium lactate 4 days calcium chloride
...nal fluid: colorless, protein, ... mg./100 cc.	Calcium chloride, 2 Gm. for 2 days; dihydrotachysterol, 1.25 mg. for 1 day	6.6 11.1	... 5.6	... 5.7	.. ..	4.1 ...	....	Before 2 days after
...nal fluid: slightly yellow, ...otein, 50 mg./100 cc.	Calcium chloride, 3 Gm. for 2 days; calcium chloride, 2 Gm. for 2 days; calcium chloride, 1 Gm. for 4 days; dihydrotachysterol, 2.5 mg. for 2 days; dihydrotachysterol, 1.25 mg. for 4 days	6.9 9.0 10.9	11.9 8.4 7.2	9.1	31	... ...	*p*H, 7.55 Carbon dioxide, 24 mEq./L. ..... *p*H, 7.40 Carbon dioxide, 18 mEq./L.	Before 1 day after 4 days after
...nal fluid: colorless	Calcium chloride, 2 Gm. for 3 days; calcium chloride, 1 Gm. for 4 days; dihydrotachysterol, 1.25 mg. for 7 days	7.8 10.0	4.6 6.0	7.0 ...	29 ..	... ...	....	Before 3 days after

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Included in the table are data on the patients concerning the sex, weight, birth history, symptoms and course in the hospital, the therapy employed and the results of relevant chemical determinations. As may be seen, there was a preponderance of male infants. Most of the patients were of normal weight, but 3 weighed less than 2,500 Gm. Two other infants born after eight months' gestation weighed 2,900 and 3,400 Gm., respectively. Both were edematous. The birth history of most of the infants was normal. Three infants had somewhat delayed respirations; 2 had a serious delay in breathing. Symptoms were noted on the first day of life ten times and on the second day six times. Two infants had symptoms for the first time on the eleventh and the thirteenth days of life, respectively. Edema and vomiting were usually seen early. Convulsions occurred both early and late.

The data in table 2 indicate that the reason for admission among almost one half of the infants was convulsions and, among a slightly smaller number, vomiting. In 3 patients both convulsions and vomit-

TABLE 2.—*Chief Symptoms Before Admission to Hospital in 33 Patients with Tetany of the Newborn (Children's Hospital Series)*

Symptom	Number of Patients
Convulsions	15
Vomiting	11
Convulsions and vomiting	3
Cyanosis	1
Scleredema	1
Other illness	2

ing were prominent symptoms. Cyanosis was the most notable symptom once. Severe edema, designated in this instance as scleredema, was the presenting sign in 1 patient. In 2 children with major illnesses erythroblastosis and tracheoesophageal fistula, hypocalcemia was present. One baby who vomited and had edema was admitted for observation because 2 previous infants of the mother, a diabetic patient, had died soon after birth. A low serum calcium level was demonstrated.

In table 3 are listed the symptoms observed. They are arranged in a manner similar to that used in a previous communication.[1] The commonest symptom was vomiting, often of a severity sufficient to dominate the clinical picture. Convulsions were next in frequency. Peripheral nervous system manifestations were noteworthy by their rarity. The presence of the Chvostek sign was described twelve times but it was not always sought. Disturbances in ocular movements and respiration were mentioned infrequently. Their significance is difficult to assess in children at an age when these functions are not yet stabilized. Both lethargy and irritability were noted, at times alternating in the same patient. Edema was seen in 16 patients and was of severe

degree in 9. It is of interest in view of the frequency of vomiting that only 1 infant was dehydrated. Twelve of the babies exhibited cyanosis to a variable degree. This sign was listed only when it occurred independent of convulsions. Hemorrhagic manifestations included hematemesis, melena, hemoptysis and petechiae of the skin. The significance of the cardiac abnormalities observed is difficult to assess in infants of

TABLE 3.—*Incidence of Manifestations in 33 Infants with Tetany of the Newborn (Children's Hospital Series)*

	Number of Patients
I. Changes in neuromuscular function	
A. Central effects	
Convulsions	22
Spasticity	5
Lethargy	6
Irritability	15
B. Peripheral effects	
Carpopedal spasms	2
Inspiratory stridor	5
Hoarse cry	3
Presence of Chvostek's sign	12
Ankle clonus	6
C. Ocular effects	
Nystagmus	3
Conjugate deviations of eyes	4
II. Changes in autonomous functions	
Respiratory system	3
Heart	
Bradycardia	1
Tachycardia	1
Systolic murmur	3
Gastroenteric tract	
Vomiting	28
(Hematemesis)	(6)
(Blood in stools)	(4)
Abdominal distention	3
Skin	
Cyanosis	12
III. Changes in hydration	
Edema	
Severe	9
Mild	7
Dehydration	1
IV. Hemorrhagic manifestations	
Hematemesis	6
Blood in stools	4
Other	2

this age. In no child was organic heart disease apparent. A case history which illustrates many of the common symptoms follows.

CASE 9.—T. C., a full term infant, was delivered by low forceps breech extraction but breathed well. When put to the breast, he vomited after each feeding. The stools were normal. On the sixth day of life the child became irritable and a tremor of the hands and feet developed. On the ninth day, five generalized convulsions occurred. On his admission to the hospital on the following day the child was alert but irritable. The face, hands and feet were edematous. In spite of the vomiting he weighed 150 Gm. more than at birth. The deep reflexes were increased and ankle clonus was present. The arms and legs shook almost con-

stantly. The serum calcium level was 7.6 and the phosphorus level 8 mg. per hundred cubic centimeters; the phosphatase activity measured 8 Bodansky units. Rapid cessation of vomiting and irritability and disappearance of the edema followed therapy with calcium chloride. Two days after his admission to the hospital, the serum levels of both calcium and phosphorus were normal.

Many of the signs and symptoms, such as vomiting, convulsions, lethargy and irritability, suggest birth trauma of the central nervous system, cerebral anoxia or meningitis. The infants as a group were more responsive than children with intracranial disease. Their Moro and sucking reflexes were good, the cry hoarse—not a high pitched cerebral cry or moan—and they usually nursed well. The cerebrospinal fluid in the 15 instances it was examined was normal or nearly so. Doubtful clinical evidence for subdural hemorrhage was present once. At postmortem examination a small subdural hemorrhage was observed in one patient and in another minimal cerebellar and subarachnoid hemorrhages. None of the infants who survived presented any symptoms indicative of residual cerebral trauma. The history of an infant for whom the diagnosis of birth trauma was entertained follows:

CASE 12.—J. S. was born spontaneously at full term but appeared lifeless at birth. He failed to breathe spontaneously and was placed in a respirator. He cried only after two hours and then weakly. Somewhat later, twitchings of the extremities occurred. On his admission to the hospital at the age of 2 days he was observed to be a well formed, slightly icteric, mildly cyanotic infant. The Moro reflex was exaggerated and the respirations of cog-wheel type. Sustained ankle clonus and the Chvostek sign were present; the grasp and sucking reflexes were normal. There was slight generalized edema. The cerebrospinal fluid was examined and demonstrated to be slightly xanthochromic, with 2 white blood cells per cubic millimeter and a protein content of 84 mg. per hundred cubic centimeters. The blood serum calcium was 7.0 and the phosphorus 5.4 mg. per hundred cubic centimeters. In the hospital the patient vomited persistently. He was treated with calcium chloride. The twitchings ceased almost at once, but vomiting of some feedings continued for several days. After two weeks' stay in the hospital, he was discharged in good health.

The response to calcium therapy makes it seem that, although birth trauma may have been present, tetany was a cause of many of the child's symptoms.

Persistent vomiting and hematemesis may suggest a congenital malformation of the intestinal tract, meconium ileus, peptic ulcer or melena neonatorum.

CASE 4.—A gastrointestinal roentgenogram of J. S. showed a long delayed retention of iodized oil in the stomach and upper segment of the duodenum, with little air in the remainder of the intestine. Because of this finding a laparotomy was performed and apparent spasm of the upper part of the duodenum without organic obstruction was observed. The serum calcium content was 7 mg. per hundred cubic centimeters. The child died and permission for necropsy was not obtained.

CASE 13.—T. was the third child of a diabetic mother. Because the 2 previous infants had died almost immediately after birth, this baby was brought to the Children's Hospital an hour after she was born. The delivery was by cesarean section after eight months' gestation. The child weighed 3,400 Gm. On arrival she looked healthy but edematous. No congenital malformations were apparent. The blood sugar content was carefully followed and, though low at times, never fell to true hypoglycemic levels. The baby was offered dextrose solution by mouth at frequent intervals. She took the first three feedings well and then began to vomit. On the second day of life twitching of one leg was noted. Later, the baby became alternately drowsy and irritable and exhibited tremors of the hands. No stool was passed for forty-eight hours, and the abdomen became distended. In a roentgenogram of the abdomen multiple dilated loops of small bowel and a collection of air in the proximal portion of the colon were seen. A barium sulfate enema revealed that the rectum and sigmoid were apparently somewhat underdeveloped and that the colon still contained much meconium. Meconium ileus was suggested as a diagnosis. Following a rectal examination, the baby passed mucus

TABLE 4.—*Distribution of Values for Calcium, Phosphorus, Phosphatase, Nonprotein Nitrogen and Serum Protein in 33 Infants with Tetany of the Newborn (Children's Hospital Series)*

Constituent	I	II	III	IV	Total No. of Values
Calcium, mg./100 cc.	< 7	7 to 8	8 to 9	> 9	..
Number of values	9	16	8	0	33
Phosphorus, mg./100 cc.	..	< 6	6 to 8	> 8	..
Number of values	..	7	8	10	25
Phosphatase, Bodansky units	<10	10 to 12	12 to 20	>20	..
Number of values	11	2	1	0	14
Nonprotein nitrogen, mg./100 cc.	<40	40 to 50	50 to 60	>60	..
Number of values	10	5	1	5	21
Serum protein, Gm./100 cc.	< 4.0	4.0 to 5.0	5.0 to 6.0	> 6.0	..
Number of values	2	6	4	0	12

and firm meconium and had normal stools thereafter. Calcium therapy brought about prompt cessation of tremors and irritability, but the vomiting continued for twenty-four hours. On the second day of life the serum calcium level was 7.4 and the phosphorus level 7.8 mg. per hundred cubic centimeters. By the sixth day the serum calcium content had risen to 10.5 mg. per hundred cubic centimeters; the patient had lost 750 Gm. and the edema had disappeared. Inspissation of meconium may explain some of the abdominal distention and vomiting, but tetany was apparently the chief cause of the infant's difficulty. She has continued to develop and gain well at home.

In table 4 the important chemical data are arranged in broad intervals for ease of inspection. It may be seen that about one fourth of the calcium values were less than 7, one-half between 7 and 8 and one-fourth between 8 and 9 mg. per hundred cubic centimeters. The value for serum phosphorus was above 8 mg. per hundred cubic centimeters in 10 of the 25 tests. The phosphatase activity was normal in all but 1 infant, a child with erythroblastosis and severe hepatic injury. The nonprotein nitrogen content of the serum in three fourths of the infants

was in the same range as that determined later in a control series, but there were five values over 60 mg. per hundred cubic centimeters. The serum protein levels tended to be lower than in the control series but not to a statistically significant degree.

The data of table 1 reveal no demonstrable association among calcium, protein, phosphorus or nonprotein nitrogen levels in the serum. As to the calcium versus protein relationship, the lack of an association is illustrated by cases 13 and 23; in case 13 the calcium level rose from 7.4 to 10.5 mg. with practically no change in the level of the protein, which remained below 4 Gm. per hundred cubic centimeters. In case 25 an increase of calcium from 6.4 to 9.8 mg. was accompanied by a drop of protein from 5.9 to 5.5 Gm. per hundred cubic centimeters. As to the calcium versus phosphorus relationship, one may cite, on the one hand, cases 22 and 24, with calcium values of 6.4 and 5.0 and normal levels of phosphorus of 5.0 and 5.8 mg., and, on the other, cases 3, 9 and 21, with somewhat higher calcium values and phosphorus values of 8.2, 9.0 and 9.7 mg., respectively. A similar lack of parallelism with regard to the calcium versus nonprotein nitrogen relationship is demonstrated by cases such as 10 and 17, with high nonprotein nitrogen levels of 87 and 98 and calcium levels of 6.6 and 8.8 mg. per hundred cubic centimeters, respectively.

STUDIES IN A NURSERY FOR THE NEWBORN

The foregoing experience in a children's hospital suggested the importance of a study of a group of infants in a nursery for the newborn with a view toward discerning those clinical manifestations apt to be associated with hypocalcemia. Such a study was carried out intermittently from May 1946 to April 1947 in the nursery for the newborn of the Cincinnati General Hospital. Only full term infants were included. On the basis of the hypothesis of a broad symptomatology of tetany, a card was made out listing the following symptoms: disturbances in the manner of breathing and feeding and the presence of vomiting, edema, drowsiness, stiffness, irritability, convulsions, crowing, Chvostek's sign and ankle clonus. For each infant in whom the severity, persistence or multiplicity of these symptoms was considered significant, 2 infants lacking such manifestations were observed. Thus, two groups were accumulated, one of 24 infants with possible manifestations of tetany and another of forty-eight infants without such signs. On all subjects, determinations of calcium content, and on most also of phosphorus and nonprotein nitrogen levels, were made. On a smaller group sufficient blood for serum protein and phosphatase determinations was available.

It should be emphasized that this study was of a preliminary and orienting nature. Many newborn infants are cared for in the nursery

and most of them stay only five days. A rotating group of resident physicians is responsible for their care. A routine examination is performed on the first and on the fourth days of life. Additional examinations are made when untoward signs or symptoms are reported by a nurse. The infants who were stated to have signs of tetany either on the basis of the results of a routine physical examination or on the basis of the report of a nurse were observed daily thereafter, but not the control infants. The comparison of the groups left much to be desired, since the two groups of infants were not examined with equal

TABLE 5.—*Incidence of Tetanic Manifestations Among Infants in a Nursery for the Newborn (Cincinnati General Hospital Series)*

Symptoms	48 Normal Controls	Infants with Tetanic Manifestations: 24 Full Term, with Mild Symptoms	9 Full Term, Seriously Ill	12 Premature
I. Changes in neuromuscular function				
Convulsions	0	1	4	1
Spasticity	0	11	3	6
Lethargy	3	3	3	6
Irritability	9	15	2	2
High pitched cry	0	0	2	1
Stridor	3	7	0	0
Chvostek sign	2	9	0	2
Ankle clonus	0	6	2	0
II. Changes in autonomous functions				
Respiration	1	3	4	6
Cyanosis	0	0	4	3
Tachycardia	0	1	0	0
Systolic murmur	0	0	0	1
Vomiting	10	12	5	7
(Vomiting blood)	0	1	3	3
III. Changes in hydration				
Edema	2	10	4	7
(Scleredema)	0	0	1	5
IV. Hemorrhagic manifestations				
Hematemesis	0	1	3	3
Other	0	0	3	2

thoroughness. Signs such as Chvostek's, which depend on relaxation of the infant, were probably often missed when only a single examination was made.

During the time of the study 9 ill infants with signs suggestive of tetany were transferred to the pediatric service. They are grouped separately. A group of 12 premature infants, with a wide range of symptoms possibly related to tetany, was also examined.

The incidence of clinical manifestations is listed in table 5 with the four groups arranged in order of increasing frequency and severity of signs. All symptoms listed for the control group were of minor degree and inconstant in nature. Irritability and vomiting were fairly common. In a few instances, lethargy, stridor and edema were described. Two babies showed the Chvostek sign, and 1 had slight respiratory

TABLE 6.—*Symptoms, Course and Chemical Data in 14 Pati*

Case No.	Sex	Weight at Birth, Gm.	Age at Onset, Days	Birth History	Symptoms and Course
G 1	M	3,300	0	Normal	Cyanosis; irritability; rapid breathing; high pitched cry; brown vomitus; rapid improvement followed calcium treatment
G 2	M	2,600	0	Normal	Jaundice; enlargement of liver, poor breathing; spasticity; lethargy; died on second day
G 3	F	2,800	1	Normal	Bloody sputum; rigidity; irritability; convulsions; continued rigidity during 1 month's stay in hospital
G 4	M	2,550	1	Normal	Poor breathing; hematemesis; edema; bradycardia; died on second day
G 5	M	3,050	1	Slight delay in breathing	Persistent vomiting during 10 days' stay in hospital
G 6	F	2,600	2	Normal	Lethargy; cyanosis; edema (scleredema); poor breathing; hematemesis; petechiae; died on fifth day
G 7	M	3,400	2	Protracted labor	Spasms of face and extremities; lethargy; edema; high pitched cry; vomiting; poor breathing; died on fifth day
G 8	F	3,100	4	Normal	Vomiting and convulsions; cyanosis; improved for 1 day after calcium therapy; sudden collapse on sixth day; mass developed in left flank; died
G 9	M	2,800	10	Normal; loss of blood from laceration of scalp	Cyanosis; edema; convulsions; some improvement, but recurrence of convulsions while on treatment with calcium lactate; permanent recovery with calcium chloride
G 10	M	2,350	0	8 months' gestation; normal	Lethargy; cyanosis; spasticity; edema (scleredema); poor breathing; premortem hematemesis and petechiae of skin; died on second day
G 11	M	2,350	0	8 months' gestation; normal	Lethargy; cyanosis; spasticity; edema (scleredema); poor breathing; premortem hematemesis and petechiae of skin; died on second day
G 12	M	2,100	0	8 months' gestation; normal	Poor breathing; cyanosis; rigidity and hematemesis on third day; died on sixth day
G 13	M	2,300	2	8 months' gestation; normal	Severe edema (scleredema); cyanosis of limbs; high pitched cry; after 3 days, spontaneous slow improvement
G 14	M	1,320	4	7 months' gestation; normal	Severe edema; vomiting; systolic murmur; edema increased until tenth day of life; respiratory standstill after transfusion; edema rapidly subsided following antitetanic therapy

difficulty. In the group of infants with mild signs, irritability, vomiting —often protracted—spasticity and edema were the commonest symptoms. Seven had a stridor; 3 were lethargic, and 3 had respiratory difficulty. In 9 instances the Chvostek sign was present and in 6 ankie clonus. One child with a massive hemorrhage into the anterior chamber of the left eye had a convulsion but no other sign suggestive of tetany. Normal values for calcium, phosphorus and nonprotein nitrogen of the serum were determined for this child. Among the seriously ill patients, dealt with in detail in table 6, vomiting, convulsions, poor

Tetany of the Newborn (Cincinnati General Hospital Series)

Comment	Therapy	Results of Laboratory Tests					Time of Sample Relative to Start of Therapy
		Calcium, Mg./ 100 Cc.	Phosphorus, Mg./ 100 Cc.	Non-protein Nitrogen, Mg./ 100 Cc.	Protein, Gm./ 100 Cc.	Other Results	
.....	Calcium chloride, 2 Gm. for 3 days	7.6	4.4	44	...	..	Before, 2 days no therapy
		7.8	5.2	66	...	..	Before, 4 days no therapy
		11.0	6.1	43	...	..	7 days therapy
ythroblastosis; necropsy: patic necrosis and staining basal ganglions	None	8.2	12.0	48	4.8	Bilirubin, 33 mg./100 cc.	Before
ephalogram: general cere- al atrophy	Calcium lactate, 4 Gm. for 2 days	7.0	4.8	42	...	..	Before
		9.0	7.2	..	...	..	2 days calcium lactate
ropsy: large subarachnoid morrhage; pneumonia	None	8.0	8.6	88	...	..	Before
.....	None	8.6	6.8	32	...	..	Before
ropsy: pulmonary atelec- sis but no intracranial morrhage	None	8.8	7.4	54	...	..	Before
ropsy: minimal subarach- id hemorrhage; pulmonary electasis	None	7.4	8.3	50	...	..	Before
nal fluid; colorless, protein mg./100 cc.; necropsy: rombosis of right renal in with infarction of kid- y	Calcium chloride, 3 Gm. from fourth day to death; dihydrotachysterol, 2.5 mg. for 1 day	7.6	15.8	86	...	..	Before
		14.4	9.4	83	...	..	2 days therapy
.....	Calcium lactate, 4 Gm. for 2 days; calcium chloride, 1 Gm. for 7 days	6.4	...	..	...	..	Before
		5.2	...	..	...	..	4 days calcium lactate
		10.4	...	..	...	..	4 days calcium chloride
ropsy: widespread hemor- hages of skin and internal rgans	Calcium lactate, 3 Gm.	7.8	6.2	56	4.2	..	After 1 Gm. calcium lactate orally
ropsy: widespread hemor- hages of skin and internal rgans	Calcium lactate, 3 Gm.	7.2	5.2	54	4.4	..	After 1 Gm. calcium lactate orally
ropsy: subdural hematoma left occipital region	None	7.0	7.6	..	...	..	.....
.....	None	6.7	6.6	76	...	..	Before
.....	Calcium chloride, 2 Gm. for 2 days; calcium lactate, 3 Gm. for 3 days	6.7	5.7	46	4.6	..	Before

breathing, cyanosis and edema (once called scleredema) were common. Hematemesis, other hemorrhagic manifestations, spasticity, lethargy, a high pitched cry and ankle clonus occurred in 2 or 3 instances each. Of the premature infants, 5 were seriously ill and are referred to in detail in table 6. They contribute a disproportionate share of the manifestations listed in table 5. In the patients as a whole, edema—in 5 instances sufficiently tense to be classed as scleredema—vomiting, spasticity, lethargy and poor breathing were prominent symptoms. Hemorrhagic manifestations and cyanosis followed in order of frequency.

In tables 7 to 10 are presented the results of the chemical determinations in a summary manner. It may be seen in table 7 that of 48 control infants only 1 had a calcium level below 8 (actually 7.4) mg. and 4 between 8 and 9 mg. per hundred cubic centimeters of serum.

TABLE 7.—*Distribution of Values for Calcium, Phosphorus, Nonprotein Nitrogen and Serum Protein in 48 Control Newborn Infants (Cincinnati General Hospital Series)*

Constituent	I	II	III	IV	Total No. of Values
Calcium, mg./100 cc.	< 8	8 to 9	9 to 10	>10	..
Number of values	1	4	20	23	48
Phosphorus, mg./100 cc.	..	< 6	6 to 8	> 8	..
Number of values	..	23	22	2	47
Nonprotein nitrogen, mg./100 cc.	<40	40 to 50	50 to 60	>60	..
Number of values	26	12	3	1	42
Serum protein, Gm./100 cc.	< 1	4 to 5	5 to 6	> 6	..
Number of values	0	1	7	6	14

TABLE 8.—*Distribution of Values for Calcium, Phosphorus and Nonprotein Nitrogen in 24 Full Term Infants with Signs of Tetany (Cincinnati General Hospital Series)*

Constituent	I	II	III	IV	Total No. of Values
Calcium, mg./100 cc.	< 8	8 to 9	9 to 10	>10	..
Number of values	3	13	5	3	24
Phosphorus, mg./100 cc.	..	< 6	6 to 8	> 8	..
Number of values	..	10	4	6	16
Nonprotein, mg./100 cc.	<40	40 to 50	50 to 60	>60	..
Number of values	10	2	2	3	17

TABLE 9.—*Distribution of Values for Calcium, Phosphorus and Nonprotein Nitrogen in 9 Seriously Ill Infants with Tetany (Cincinnati General Hospital Series)*

Constituent	I	II	III	IV	Total No. of Values
Calcium, mg./100 cc.	< 7	7 to 8	8 to 9	> 9	..
Number of values	1	4	4	0	9
Phosphorus, mg./100 cc.	..	< 6	6 to 8	> 8	..
Number of values	..	2	2	4	8
Nonprotein nitrogen, mg./100 cc.	<40	40 to 50	50 to 60	>60	..
Number of values	1	3	2	2	8

Only 2 of the infants had a serum phosphorus value above 8 mg. per hundred cubic centimeters. The nonprotein nitrogen level in most infants was below 40 mg., in 13 between 40 and 50 mg., in 3 between 50 and 60 mg. and in 1 above 60 mg., per hundred cubic centimeters of serum, a distribution such as has been observed in other series of normal newborn infants. The serum proteins were also in the range

usually seen. Of the 24 infants stated to show tetanic manifestations (table 8), 3 had serum calcium values below 8 mg. and 13 between 8 and 9 mg., per hundred cubic centimeters; one third of the values were higher. In 2 of 16 determinations a phosphorus value above 8 mg. and in 3 of 17 a nonprotein nitrogen level above 60 mg. per hundred cubic centimeters of serum were observed. Nine seriously ill full term infants (table 9) had serum calcium values below 9 mg. per hundred cubic centimeters. In 4 a phosphorus content above 8 and in 2 a nonprotein nitrogen value above 60 mg. were observed. In all 12 premature infants (table 10) the calcium level was below 9 mg. per hundred cubic centimeters; but no phosphorus value above 8 was determined. The nonprotein nitrogen was between 50 and 60 mg. per hundred cubic centimeters in 6, and above 60 in 2, of the premature infants.

A comparison of the chemical data in all four groups is of great interest. It may be seen that the 24 full term infants with mild signs

TABLE 10.—*Distribution of Values for Calcium, Phosphorus and Nonprotein Nitrogen in 12 Premature Infants with Signs of Tetany (Cincinnati General Hospital Series)*

Constituent	I	II	III	IV	Total No. of Values
Calcium, mg./100 cc.	< 7	7 to 8	8 to 9	> 9	..
Number of values	3	4	5	0	12
Phosphorus, mg./100 cc.	..	< 6	6 to 8	> 8	..
Number of values	..	5	6	0	11
Nonprotein nitrogen, mg./100 cc.	<40	40 to 50	50 to 60	>60	..
Number of values	2	1	6	2	11

of tetany had a tendency toward lower calcium values than the control infants. The difference in distribution between the two groups is statistically highly significant. A trend toward even lower calcium values is apparent in the full term infants who were seriously ill and the premature infants. With respect to the phosphorus levels, the differences are much less clear. Among the full term infants a trend to values above 8 mg., with increasing number and severity of symptoms, is suggested, but high phosphorus values were not seen in the premature infants. This is in consonance with the data of Willi.[8] Elevated levels of nonprotein nitrogen were observed in increased numbers in the groups with severe manifestations. An insufficient number of serum protein determinations was performed to allow comparisons.

A comparison of the data on the control infants with those on normal infants reported in the literature is vitiated by the fact that in none of the other series were infants with possible tetanic manifestations eliminated. The largest collection of data, by Todd and his associates,[12]

12. Todd, W. R.; Chuinard, E. G., and Wood, M. T.: Blood Calcium and Phosphorus in the Newborn, Am. J. Dis. Child. **57**:1278 (June) 1939.

obtained on 639 infants, gave a mean calcium value of 10.15 mg. with a standard error of 0.022 mg. From these data a standard deviation of 0.76 mg. may be calculated.[13] Assuming the conventional limits of ± 2 times the standard deviation, the range of 8.63 to 11.67 mg. would encompass 90 per cent of all infants studied, of course including those with a mild tendency to tetanic manifestations (see group II, table 8). For phosphorus, these authors give a mean value of 6.03 ± 0.021 mg. per hundred cubic centimeters, from which a standard deviation of 0.69 mg. may be calculated. Thus, the range of 4.65 to 7.41 mg. per hundred cubic centimeters would include 90 per cent of the values of a "normal" population of newborn infants. Data on other series summarized by Todd and his associates gave similar values.

Nine of the full term and 5 of the premature infants were seriously ill. The pertinent data on both groups, the full term infants first, are presented in table 6. The infants are arranged in order of age at onset of symptoms. A comparison with the series seen at the Children's Hospital is of interest. Here also the infants were predominantly male and most had been born without difficulty. The age at onset of symptoms varied from a few hours to ten days after birth. The same wide range of symptoms occurred in both series, but the frequency of hemorrhages was even more impressive in the patients seen at the General Hospital. A high proportion of the infants died. One had severe erythroblastosis; 2 had massive intracranial hemorrhage, and 2 premature infants had widespread hemorrhages. In 1 child a thrombosis of the right renal vein occurred. In 2 infants no adequate morphologic cause of death was discovered.

In several of the infants the significance of the hypocalcemia appears to be extremely doubtful. Two of the cases, however, clearly indicate the possible importance of hypocalcemia in disturbances of the neonatal period.

CASE G 9.—EV. exemplifies the failure of calcium lactate treatment. The infant was born at full term but had a laceration of the scalp at delivery and lost a considerable amount of blood. On the tenth day of life he appeared cyanotic and edematous and had a generalized convulsion. Four grams of calcium lactate was given for two days but another convulsion occurred. The medication was changed to calcium chloride in a dose of 1 Gm. daily, and the patient improved promptly. The serum calcium was 6.4 mg. per hundred cubic centimeters at the time of the first convulsion and 5.2 mg. after treatment with calcium lactate, but rose to 10.4 mg. after four days of calcium chloride therapy.

13. Unfortunately, the authors presented in their tables the mean and the extreme values, rather than a statistical description of their data. But since the standard error of the mean, given by them in the summary of their paper, is equal to the $\frac{\text{standard deviation}}{\sqrt{\text{number of observations}}}$ the standard deviation is readily calculated.

CASE G 14.—The case of Da. illustrates the danger of the administration of citrated blood to an infant with hypocalcemia. The infant, born after seven months' gestation, weighed 1,320 Gm. Breathing was somewhat delayed. On the fourth day of life he became edematous and began to vomit. By the tenth day, edema had increased to extreme proportions and he weighed 1,550 Gm. At that time a systolic cardiac murmur became audible. On the next day, while 35 cc. of blood was being given intravenously, the infant suddenly stopped breathing and the heart rate dropped to 15 per minute. After ten minutes of resuscitative measures the infant recovered from this episode but was extremely irritable thereafter. Two grams of calcium chloride was given daily for two days, followed by calcium lactate. The edema rapidly subsided; the vomiting ceased; the systolic murmur disappeared, and the further course was uneventful. On the tenth day when edema was extreme, the calcium was 6.7 mg., the phosphorus 5.7 mg., the nonprotein nitrogen 46 mg. and the protein 4.6 Gm., per hundred cubic centimeters of serum. It is likely that in the presence of hypocalcemia, the formation of an un-ionized complex of serum calcium with the citrate contained in the blood administered was the cause of the respiratory standstill.

COMMENT

Chemical Data.—The data presented indicate that serum calcium values below 9 mg. are rare in normal newborn infants. Among the group of infants stated to show signs of mild tetany, low calcium values were frequent but by no means universal. In a survey of the material as a whole, the impression is gained that severity of symptoms and depression of calcium levels tended to parallel each other. On the other hand, it is noteworthy that manifest tetany occurred with calcium values between 8 and 9 mg. per hundred cubic centimeters. The levels of one fourth of the patients in the Children's Hospital group fell in this range. Phosphorus values above 8 mg. are extremely uncommon in normal newborn infants. Such levels occurred in about one third of the infants with clinical tetany. One may conclude that levels of calcium above 9 mg. make the diagnosis of tetany unlikely. A high phosphorus value adds considerable weight to the diagnosis.

The phosphatase values were normal in all infants, with the exception of one who had hepatic damage from erythroblastosis. This determination serves to differentiate neonatal tetany from the rachitic tetany of young infants. In oriental countries, where maternal osteomalacia is common, rickets and tetany occur within the neonatal period.[14] In the United States, rachitic tetany is rare in infants less than 3 months of age. However, cases of rachitic tetany have been seen at the Children's Hospital in Cincinnati in infants as young as 5 weeks. It is particularly likely to occur in rapidly growing premature infants or twins.

14. Snapper, I.: Medical Clinics on Bone Diseases: A Text and Atlas, New York, Interscience Publishers, Inc., 1943.

Considerable elevations of the nonprotein nitrogen levels occurred in the infants with hypocalcemia. They were transient and did not signify renal anomalies. The presence of a renal anomaly may be suspected with persistent elevation of the nonprotein nitrogen value. Such infants tend to exhibit recurrent hypocalcemia which is refractory to treatment. Two examples have been reported by Snelling,[11] and several have been observed at the Children's Hospital in Cincinnati.

A trend to low values of serum protein was apparent in the infants with neonatal tetany as compared with the control infants. It may be thought that the change was a factor in the lowering of the calcium values and in the causation of edema. However, no relation is discernible in individual children between the levels of calcium and protein, and the edema usually responded dramatically to therapy with calcium chloride. Treatment of the edema by administration of blood or plasma, because of their citrate content, carries with it the danger of further reduction of available calcium.

Causation of Tetany of the Newborn.—The occurrence of hypocalcemia in the neonatal period may be thought to be related to a variety of factors. The differing histories of the infants reported on in the literature and here support such a concept. Among the variety of factors, one may cite (1) vomiting, with attendant hypochloremic alkalosis, (2) hyperventilation with respiratory alkalosis, perhaps caused by fever or irritation of the respiratory center, or (3) renal factors, such as a general immaturity of function or a specific renal disturbance concerning calcium and phosphorus. These factors, singly or combined, may be the cause of hypocalcemia in some instances. Nevertheless, there remains a large group of cases without change of electrolyte distribution and without retention of nonprotein nitrogen. They constitute the basis for the hypothesis that insufficiency of the parathyroids is the main etiologic factor of the syndrome. As an explanation of this insufficiency, hemorrhages into the parathyroids was cited by Erdheim and Yanasse [15] and a functional insufficiency of the glands by Bakwin.[9] Hemorrhages into the parathyroids have been demonstrated at necropsy in infants with tetany, but they have also been observed in infants who died from other causes.[15]

The assumption of a functional insufficiency is in agreement with the usually self-limited course of the disease. As to its cause, immaturity of the parathyroid glands, although unsupported by histologic evidence, has appeared to many observers as a plausible explanation. An alternate or additional factor may be represented by the maternal influence on the parathyroids of the infant, in the direction of a suppression of their function. This hypothesis gains support from experi-

15. Cited by Shelling, D. H.: The Parathyroids in Health and in Disease, St. Louis, C. V. Mosby Company, 1935, p. 40.

ments on rats in which an elevated calcium level was maintained during pregnancy by means of injections of parathyroid extract, resulting in severe hypocalcemia in the offspring.[16] In the same connection, the case of hypocalcemic tetany in an infant born of a mother with hypercalcemia associated with an adenoma of a parathyroid gland may be cited.[17] It may be, then, that variability in the degree of the hypertrophy of the parathyroids occurring during pregnancy is a determining factor in the incidence of neonatal tetany. This view has been held by Hoffmann,[18] and Bakwin.[9] The hypothesis of a primary parathyroid origin by no means excludes an important role of other factors. They may be operative when hypocalcemia occurs as a complication of some unrelated primary disease. The coincidence of erythroblastosis and hypocalcemia, noted in this series and repeatedly since, may point in this direction.

The possible effect of the diet should be considered. Intake of cow's milk was suggested by Bakwin [9] as a cause of the preponderance of neonatal tetany in the United States. The frequency of the condition in the first forty-eight hours of life observed in this series, and by Willi [8] in Europe, lends no support to this hypothesis.

The similarity in type and distribution of symptoms makes the discussion on the manifestations of the postacidotic state of infantile diarrhea [1] relevant and, in the main, applicable here. That discussion may be briefly summarized as indicating a broad symptomatology of tetany, including clinical manifestations of the neuromuscular system, edema, a variety of disturbances of autonomous functions—including, among others, respiration, gastrointestinal motility, cardiac action, temperature and vasomotor control—and in chronic tetany trophic disturbances. In addition, suggestive evidence was cited for an intimate connection between hemorrhagic phenomena and hypocalcemia. Reference was also made to a tendency noted by earlier observers for prevalence of central nervous system signs and paucity of peripheral signs in young infants. Thus, among infants in the postacidotic state, as among those reported on here, convulsions were in the foreground. The two groups differ in that the incidence of edema appears greater in the present series, a circumstance possibly related to the immaturity of renal function in newborn infants. Vomiting, the commonest symptom in the newborn series, could not be assessed in the postacidotic group, because of the underlying illness, gastroenteritis. Hemorrhagic manifestations

16. Schwartzer, K.: Ueber die Blutkalkregulation beim Neugeborenen, Klin. Wchnschr. **19**:107, 1940.

17. Friderichsen, C.: Hypocalcämie bei einem Brustkind und Hypercalcämie bei der Mutter, Monatsschr. f. Kinderh. **75**:146, 1938.

18. Hoffmann, F.: Ueber die Darstellung und den Nachweis des Nebenschilddrüsenhormons im Schwangerenblut, Arch. f. Gynäk. **153**:181, 1933.

appear to be commoner in the newborn infants. The possibility of a multiple causation—hypoprothrombinemia, capillary fragility and anoxic damage—renders any interpretation of this circumstance hypothetic. Nevertheless, the correlation between hemorrhagic tendency and hypocalcemia appears impressive. In several cases of postacidotic tetany the weight of the evidence pointed toward tetany as the cause of intracranial hemorrhage. This relationship may not hold in the neonatal period and birth trauma, mechanical or anoxic, may well be the initial event.

Prognosis.—Consideration of the prognosis of hypocalcemia and tetany on the basis of the cases presented in the literature and here is rendered hypothetic to a large extent by the general lack of knowledge concerning the pathology and pathologic physiology of the neonatal period, so that the presence of conditions other than tetany, even though not evident by clinical or pathologic examination, must in principle be admitted in every case. Actually, in several infants, definite pathologic changes, which may well have been of determining importance, could be observed. The following discussion is offered with these reservations in mind.

If tetany of the newborn, as is the opinion of some authors, is merely the extreme of a physiologic response of newborn babies, the question arises whether infants with tetany will recover spontaneously if left untreated. A review of the literature shows that such has sometimes been the case but also that clinical symptoms and low levels of serum calcium have persisted unchanged for days or weeks and that fatalities have occurred. On the other hand, dramatic improvement has often followed the institution of calcium therapy.

The patients presented here exhibited a wide variation in the course of their disease. Consider first the infants in the Children's Hospital series: Of the 8 untreated patients, the illness in 1 had an uneventful course and in 2 a course of slow improvement; 4 infants died, and 1 was discharged unimproved. One of the infants who died had a tracheoesophageal fistula and pneumonia; another was a premature infant, and 2 were not examined post mortem. The serum calcium levels of these 4 infants were 7.4, 7.2, 7.0 and 7.4 mg. per hundred cubic centimeters, respectively. All 24 infants who were adequately treated did well. The symptoms of 3 patients continued, in 1 infant as long as thirteen days, until systematic antitetanic therapy was instituted. One patient who received only calcium gluconate and a small amount of calcium lactate did poorly in the hospital but subsequently recovered. The treated group included 1 of the immature infants, 2 who were known to be premature but who because of edema weighed more than 2,500 Gm., 1 with severe erythroblastosis and 1 child born of a diabetic mother.

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At the General Hospital, all infants in the nursery for the newborn with mild symptoms did well. Some were given calcium with apparent beneficial effect; others recovered spontaneously. Three of the 14 infants who were seriously ill showed remarkable improvement following therapy. Of the untreated infants, 1 recovered spontaneously and 1 continued to vomit during the period of observation. One infant with severe symptoms from birth on, who received only a small amount of calcium lactate, did not improve and was shown later to have cerebral atrophy. Eight infants died. One improved impressively but had a sudden collapse with thrombosis of a renal vein. One had severe erythroblastosis; 2 were premature infants who died on the second day of life; 2 had severe intracranial hemorrhage, but in 2 the pathologic observations were insignificant.

The clinical material offers a basis for the conclusion that tetany may be of serious import even when it is only a complication of some primary disease. The possibility of permanent cerebral damage has to be considered also in view of the occurrence of hemorrhagic manifestations in this series and in infants with postacidotic tetany.[1] Prompt recognition and treatment assume importance.

Therapy.—Calcium therapy is usually effective and at times dramatic in its results. Such was the experience even of the first observer, Kehrer.[2] Calcium chloride appears to be the only satisfactory agent for sustained therapy, since the lactate and gluconate have little effect. The calcium content of calcium chloride is 30 per cent, as compared with 17 per cent in the lactate and 9 per cent in the gluconate. The effect of calcium chloride is potentiated by the acidifying action of the salt, either via reduction of the blood p_H below the range at which tetany can occur or via mobilization of calcium from the bones. As in rachitic tetany, large doses should be given. The following schedule has been found satisfactory: In full term infants the initial dose is 2 Gm. of calcium chloride per day and in premature infants somewhat less. After two to three days the amount is reduced so as to avoid the development of severe acidosis. The calcium chloride is always diluted to 2 per cent strength and may be given by stomach tube. In acute conditions 0.5 to 1 Gm. of calcium gluconate, well diluted, is given intravenously but is always followed by sustaining oral therapy. It is our opinion that dihydrotachysterol has an adjuvant effect. This agent is commonly used in the treatment of permanent hypoparathyroidism. It is given orally in decreasing amounts, beginning with 2.5 mg. a day. Parathyroid extract, which had been used formerly, was avoided. Its action is abrupt and short lived, and frequently toxic effects are observed. In 1 case in this series the calcium rose to a level of 14 mg. per hundred cubic centimeters following its use, and Guild [7d] reported a death shortly after what she

described as an overdose. The serum calcium level was 20 and the phosphorus level 15 mg. per hundred cubic centimeters in her patient.

SUMMARY

Thirty-three instances of hypocalcemia in the newborn period, observed in the Children's Hospital of Cincinnati from 1937 to 1947, are reviewed.

The report includes a study which was carried out in 1946-1947 in a nursery for the newborn for the purpose of ascertaining the relationship between calcium level and clinical symptoms. Forty-eight control infants and 24 infants with signs possibly related to hypocalcemia were studied by means of physical examinations and determinations of calcium, phosphorus and nonprotein nitrogen levels of the serum. During the period of the study 9 ill infants and 12 premature infants with signs suggestive of tetany were observed in the nursery and are reported on.

The symptoms of the patients varied in time of appearance from shortly after birth to the thirteenth day of life. Most of the infants were born without difficulty and were of normal weight. Male infants predominated. The range of clinical manifestations was wide and included vomiting, convulsions, edema (in 5 instances scleredema), cyanosis and hemorrhages as the severest symptoms. At times, the symptoms of the patients suggested cerebral birth injury or intestinal obstruction. Hypocalcemia occasionally appeared as a complication of other diseases. In 3 instances it was associated with erythroblastosis fetalis; 1 infant was born of a diabetic mother, and in several instances intracranial hemorrhage was present.

In the infants with apparent tetany the serum calcium varied between 6 and 9 mg. per hundred cubic centimeters. The phosphorus was above 8 mg. in about one third of the children. Occasionally, elevations of the nonprotein nitrogen content were observed. The phosphatase values were normal. Only 5 of the control infants had a calcium level below 9 and only 2 a phosphorus level above 8 mg. per hundred cubic centimeters of serum.

Hypocalcemic tetany in the newborn period may be of serious consequence. Diagnosis and treatment with calcium are, therefore, of importance.

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Case Reports

ENCEPHALITIS AND INVOLVEMENT OF BASAL NUCLEI IN POLIOMYELITIS

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WE OCCASIONALLY see curious types of neurologic responses in poliomyelitis, but the case herein presented was unusual in that it involved the basal nuclei.

REPORT OF A CASE

H. M., a 29 year old chemist, was admitted to City Hospital on Aug. 19, 1946 with the following history.

For three years, he was stationed in India, returning to the United States on April 8, 1946. In India, he experienced episodes of chills and fever. These occurred about five times a year and were controlled with quinine, and he was ill only a short time with each seizure. It was assumed that he had malaria, but at no time was blood taken for a smear or a definite diagnosis made.

The present illness began July 6, 1946 when he felt bad, as though he were catching cold. His mother said that he complained of severe headaches one week prior to this onset. He seemed well until July 8, when he had a temperature reading of 104 F., chills and difficulty on urination. A local physician hospitalized him and made numerous smears but found no malarial parasites. The use of quinine was continued, and he became afebrile by July 10 and was discharged from the hospital.

On July 12, he complained of uncontrollable twitching of his left arm, and his physician stated that he had mild contractions of the pectoral and deltoid muscles on the left side. On the morning of July 13, he was again hospitalized, since he was having clonic contractions of his left shoulder and arm, left leg and right side of the face, which were not controlled by large doses of sedatives. At no time did he become unconscious or have a headache. His temperature was 100 F.

Consultation was had with Dr. V. W. on July 15, the report on which follows:

"His friends said that, on his return to this country about the first of the year, he was noted to have a twitching of the left side of the face. He, himself, agreed to this. During the recent bout, he began to have jacksonian-like seizures involving the right side of the face and the left side of the body. The patient had not been unconscious. His sensorium remained clear. He had no generalized convulsive movements. There was no history of abnormalities of the cranial nerves. He had not complained of headaches, vertigo or nausea and had vomited only once and that was after medication.

"There were spasmodic, irregular, jerky movements involving the right side of the face and the right leg, also the left arm, the muscles of the left side of

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the chest and, to a lesser extent, the left leg. The deep reflexes were equal on the two sides but difficult to elicit owing to the contracture of musculature previously described. Sensation appeared to be roughly normal throughout. The patient had had difficulty in voiding for the past twenty-four hours.

"I think one is forced to conclude that this patient has a bicortical irritation. The most likely source of this is some infective agent. I think that the agent is most likely to be a parasitic one. At the moment, I should strongly suspect the possibility of his having torular meningitis. The history seems incompatible with tuberculous meningitis. It seems incompatible with any pyogenic infection or with any type of neoplasm.

"It was suggested that the patient have a roentgenographic examination of his chest, that the spinal fluid puncture be repeated and particular attention paid to the question of cells and parasites and that material for suitable cultures be taken. It was not suggested, but is now, that the urine and sputum also be cultured for cryptococcus organisms.

"It is also suggested that the patient be given 100 mg. of tribromoethanol U. S. P. (avertin®) per kilogram of body weight in order to control the tiring muscular contractions. At the same time, approximately 2,000 cc. of fluid might well be given.

"The possibility of cerebral malaria was considered and thought to be unlikely. It might be advisable to give the patient small doses of epinephrine (adrenalin®) in the early part of a chill in the hope of recovering malarial parasites from the spleen.

"I do not think this clinical picture is one of quinine intoxication. The possibility of chronic scrub typhus has to be considered, but I should think it unlikely. All the subsequent tests gave normal results."

On July 15, the lumbar puncture showed 50 cells in the spinal fluid, all lymphocytes, with 53 mg. of protein and 48 mg. of sugar. No organisms were seen on direct smear.

Tribromoethanol was given to control his contractions. The contractions ceased completely but reappeared in about three hours. On July 16, another lumbar puncture showed no increased pressure and the dynamics were normal; the fluid was clear, and there were 32 cells, all lymphocytes. Protein was 37.5 mg. and sugar 59.4 mg. Cultures of the spinal fluid yielded no organisms. Cryptococcus could not be demonstrated in the spinal fluid.

Consultation was had with Dr. T. on July 26, report of which follows:

"This young male adult presented a history of several bouts of fever and chills for the past two years. His condition was diagnosed as malaria. Though no evidence was obtained that malaria had been proved microscopically, the history seemed straightforward and the fever responded to antimalarial measures. About three weeks ago (one week before his admission), the patient complained of severe headache lasting for one day. This recurred two or three times in the next few days. Finally, he had a high fever, for which he was hospitalized. Quinine was given. His temperature became normal and he was discharged from the hospital. Two or three days later, tremor, convulsive movements of the leg, hand and face developed and the patient was rehospitalized. Throughout his stay in the hospital, the temperature did not exceed 100 F. and for the past day or two has been within normal range. Vomiting occurred once; at no time was there diplopia, blindness or incontinence. The samples of spinal fluid obtained repeatedly yielded no growth on culture and showed slight increase

in cells, slight increase of protein on one occasion and low normal glucose levels; determinations of chlorides were not done. A blood cell count showed on one occasion borderline leukocytosis without eosinophilia. Cultures of the blood were negative for organisms. Spinal fluid was obtained for virus cultures and results of these have not yet been reported.

"On examination, the patient presented a clear sensorium, possibly with slight euphoria. The spleen was questionably palpated once but the finding could not be repeated. Neurologically, the patient presented frequent jerking unvolitional rhythmic movements involving all extremities. These were especially pronounced on the left side in the upper extremity, face and eyelid and less so in the right upper extremity. Deep reflexes were obtained with difficulty because of severe spasm throughout the body; nevertheless, they were present and decidedly exaggerated. There were no abnormal reflexes such as the Babinski. A clonus was present on the left. A wrist clonus was not obtained. There was no loss of sensation to pinprick in the lower extremities and the examiner was informed that on a previous examination sensation was intact.

"Although a definite etiologic diagnosis is not possible at this point, it seems clear that a diffuse lesion involving the nuclei is present. Unless virus studies show one of the specific encephalitides, it is conceivable that this is the aftermath of malaria. Multiple thromboses in the region of the nuclei could produce a picture such as this. The lack of history of exposure to schistosomiasis japonica and the absence of eosinophilia would exclude this disease. Strongyloides and Ascaris lumbricoides could give this picture in the migratory stage but are ruled out because of the time interval of exposure."

By August 2, the patient was much improved and the tremor at the time involved only the left arm. He also had some motor difficulty in his speech.

A third consultation with Dr. L. M. W. was had on August 12, the report of which is as follows:

"In spite of the statements to the contrary in the medical reports, the patient insists that he had diplopia the first week of his illness. He also experienced considerable difficulty in voiding, although he did not require catheterization.

"There was a gross shaking and nodding tremor of the head. No twitches or other abnormal involuntary movements were noted in the facial musculature. His speech was mildly dysarthric. The words were broken up into syllables emitted with a staccato-like emphasis. Occasionally, there was an explosive-like quality to his speech. There was no tremor of the protruded tongue. The fundi were negative. All extraocular movements were full. There was no nystagmus. The pupils were round and equal and reacted both to light and in accommodation, but better in accommodation.

"The most striking and obvious feature of his neurologic picture was the abnormal voluntary movements. All extremities were involved, but the left ones more than the right, and especially the left arm. The movements consisted of rapid, irregular, gross tremors with superimposed myoclonic and choreiform movements. In addition, there were gross fasciculations of the muscles of the left shoulder girdle. The tremors, as well as the other variants, were much increased in amplitude on attempted action. The action tremor became striking on forceful innervation. There was, however, no spasticity of the extremities or any rigidity. On the other hand, when the arm was passively flexed and extended, one could often demonstrate that both the extensor and the flexor muscles contracted simultaneously. This peculiarity of activity constitutes a dystonic

phenomenon which is again to be considered a fault in the integration of muscular movements.

"There were obvious wasting and associated weakness of the left deltoid muscle, the suprascapular muscles and the teres muscles on the left side. In these muscle groups, gross fasciculations were noted and on occasion there was a suggestion of fibrillatory movements. The deep tendon reflexes were active and seemingly equal in the upper extremities. There was no disturbance in any of the sensory modalities. Coordination appeared to be intact, but rapid alternate movements were performed clumsily. I regard this clumsiness as due to the faulty innervation of the muscles rather than to any fundamental disorder of synergy.

"The patient's gait was awkard but there was no staggering. There were no atrophies or weakness in the lower extremities. The deep tendon reflexes were exaggerated but no pathologic signs were elicited. There was considerable ataxia on the heel-knee test bilaterally, but more notably on the left. As stated before, there was tremor of the feet and toes, more pronounced on the left. Sensation was intact.

"*Diagnosis.*—The patient presents evidence of diffuse involvement of the subcortical cerebral mechanisms and of the spinal cord. Anatomically, the diagnosis is encephalomyelitis. The implication of the spinal cord is easily demonstrable by the focal wasting and weakness of the muscles of the left shoulder girdle. No lesion above the level of the cervical portion of the spinal cord can produce focal atrophy. The patient also stated that he had great trouble with urination the first week of his illness, which is again evidence of disease of the spinal cord.

"Furthermore, the neurologic picture points to a predominant localization of the disease in the basal ganglions of the brain. The multiple types of dyskinesias can be only a result of the disease of the basal ganglions. The intact mental functions and the absence of pyramidal signs, as well as the absence of defects in the special senses, such as vision, indicate that the cortical structures were slightly or not at all affected.

"The causation of this widespread destructive encephalomyelitis remains obscure. While such a clinical picture could possibly result from a cerebral complication of malaria, there is at present no evidence that this patient has malaria. Until the laboratory can establish the presence of parasites in the blood, the relationship of the neurologic disease to malaria remains highly conjectural. One other clue may exist regarding the causative agent, that is, the fact that the patient was in contact with horses two weeks previous to the onset of his illness. The onset, clinical course and the present neurologic residual are all compatible with the diagnosis of equine encephalomyelitis. A complement fixation test on the patient's blood serum can easily verify or disprove this possibility. The establishment of an etiologic diagnosis is, however, as far as the patient is concerned, purely academic.

"It is much too early to make any definite predictions concerning the degree of neurologic disability which will ultimately remain. Improvement is occurring and will no doubt continue for many months. A final evaluation certainly cannot be made until at least a year shall have passed. However, if I were forced to make some kind of estimate today, I should hazard the opinion that the movements will persist and possibly in their present intensity. There should be considerable increase in motor power.

"I think that it would be worth while to try the effect of the stramonium drugs on this patient in an effort to reduce his tremor."

On his discharge from the hospital in August 1946, the patient showed some weakness in the muscles of both shoulders, a slight tremor and some atrophy of the left arm.

The next information on the condition of the patient was obtained on his arrival at City Hospital on August 19. On his admission, his positive physical findings were slight atrophy of the left deltoid muscle with many fine to coarse tremors of the extremities and occasional athetoid movements and fine tremor of the tongue with no deviation on protrusion. The patient's gait was propulsive in nature when he leaned forward. Sensation was intact. The cranial nerves were not involved. The abdominal and cremasteric reflexes were present and the deep reflexes all hyperactive. There were no pathologic signs or reflexes. Muscle tests revealed 60 per cent function of the abductors of the left scapula and 50 per cent function of the deltoid, teres and latissimus dorsi muscles on the left. Lumbar puncture, blood cell count and urinalysis gave normal results.

He was started on physical therapy consisting of hot packs to and passive and active exercises of the back, arms and shoulders.

He was discharged on September 21, having shown improvement to 80 to 100 per cent function in the affected muscles. The tremor still persisted but was diminished at rest.

The physical examination on Nov. 28, 1947 showed definite pain on the inside of the shoulder joint on resistance to flexion and abduction and slight weakness of the finger and wrist extensors. The right wrist seemed almost as weak as the left on resistance. The measurements of the upper arms were 11¼ inches (29.2 cm.) on the right and 11⅛ inches (28.3 cm.) on the left. The gross tremor had disappeared, and, although the weakness described was present with attendant atrophy, the patient was able to execute all movements well.

It was important to identify the condition of the patient. We could not rule out malaria definitely, although the evidence was against an acute attack of this disease, but, with his history, there was a possibility that the malaria, the malarial treatment or both might have predisposed him to have the bizarre condition he presented, if on this condition there was superimposed some form of encephalomyelitis.

NEUTRALIZATION TESTS

Neutralization tests were done with various blood serums. Our first experiment was with a 10 per cent suspension of poliomyelitis virus in cotton rats; there were five experiments, with 2 rats in each experiment, against our 6 strains of virus that had been acclimated to cotton rats (Flexner M. V., Flexner Philadelphia, Perrysburg, Toomy, Jungeblut and Lansing strains). Two rats were protected with "early" and 2 with "late" samples of the patient's serum, and 2 were given injections as controls—30 animals in all. All the rats died.

In the first mouse experiment (Brooklyn strain of animal), we used only two strains of virus which had been adapted to the mouse (Flexner and Lansing strains) with 10 animals for each test and 0.01 per cent suspension of virus. The latter was mixed with equal parts of neutralizing serum. Thirty mice were used against each virus—10 mice were given neutralizing injections with early serum and 10 with late serum and there were 10 controls.

Of the 10 given injections of early serum against the Lansing strain, 1 died and none had paralysis; of the 10 that were given injections of late serum, 1 died and none had paralysis; of the 10 controls, 7 died and 4 were paralyzed. All this experiment showed was that there were neutralizing antibodies in both early and late serums for 0.01 per cent suspension of Lansing virus in Brooklyn mice.

In the experiment with Flexner virus, the same proportions were used; 1 of the 10 mice protected with early serum died without paralysis; of the 10 protected with late serum, 2 died, none were paralyzed; of the 10 controls, 8 died and 6 were paralyzed. The only conclusion here is that in the dilution used, both early and late serums had neutralizing antibodies. The initial serum we had been using was a relatively late serum, late in point of time of bleeding, since the patient had been sick some time before it had been withdrawn.

A third experiment was done with mice against 0.01 per cent suspensions of rat-adapted Lansing and Flexner M. V. strains. This time we fortunately obtained, from the New York Board of Health Laboratories, a small amount of serum collected earlier in the patient's illness and enough cancer-free white (CFW) mice to do the experiment. In the group tested against the Lansing strain 4 of the 10 protected with early serum died. Of the 10 protected with late serum, none died, and of the 10 controls, 9 died with paralysis, 1 of an unknown cause.

In the group tested against the Flexner strain, 1 of the 10 protected with early serum died without paralysis; of the 10 protected with late serum, none died or became paralyzed; of the 10 controls, 5 died, 2 of which were paralyzed. There was a suggestion, at least with the Lansing strain, of some difference in neutralizing value of the serums.

Later, 1.5 cc. of serum (which had been taken on July 18) was received from Dr. Irving Gordon, of the New York Board of Health Laboratories, and its neutralizing value was compared with serum obtained late in August at Cleveland City Hospital. Variable dilutions of serum and virus were used, and it was observed that a combination 50 per cent early and 50 per cent late serums against a 0.1 per cent suspension of virus protected 3 of 6 protected with early serum; all those protected with the late serum were normal; the controls all died. Cancer-free white mice were used.

In the next experiment, the strength of the virus suspension (Flexner and Lansing strains) remained fixed (1 per cent) in all experiments, and the dilution was varied: 1:10, 1:50, 1:100 and 1:200. When 50 per cent end points were considered, the percentages of mortality in the rats were as follows:

Dilution of Serum	% of Mortality	
	Early Serum	Late Serum
1:10	6.3	0
1:50	16.7	0
1:100	37.5	25
1:200	100.0	75

By logarithmic methods, the end point of early serum in neutralization to the Flexner strain was 1 to 132 and the neutralizing end point of late serum 1 to 142 with the Lansing strain of virus. A duplicate experiment was done.

Dilution of Serum	% of Mortality	
	Early Serum	Late Serum
1:10	0	0
1:50	0	0
1:100	334	15.4
1:200	100	25

Here the 50 per cent neutralizing end point was 1 to 119 for the early and 1 to 174 for the late serums.

All these computations were necessary, since it was difficult to show an actual difference between serums, the first withdrawal of blood having taken place July 18, almost three weeks after the onset of the disease. Yet despite our difficulties, there were demonstrable differences.

The next experiment was a neutralization one—virus versus late serum. Fifteen animals were used for each virus experiment, i. e., 75 animals (cotton rats) in all. They were against the viruses of eastern and western equine, St. Louis and Japanese B encephalomyelitis and lymphocytic choriomeningitis. Since there are spurious antibodies in any serums of normal 100 per cent dilution, all serums used in the experiment were diluted to 25 per cent. There were no neutralizing antibodies.

Further experimentation was impossible because of lack of material, but from the experiments conducted it seems fair enough to draw the conclusion that there was a demonstrable difference in protection values with the serum dilution titers against poliomyelitis virus.

There was no infection with the viruses of eastern or western equine or St. Louis encephalomyelitis in the district at the time.

COMMENT

The pyramidal tracts transmit motor impulses from the cortical centers of movement to the anterior horn cells of the spinal cord. From there they are conducted to the various muscles and muscle groups. Many impulses go through neighboring tracts, whose function is to strengthen and govern the activities of the pyramidal tracts. These are the extrapyramidal motor pathways which have their origin in certain parts of area 6 of the frontal lobe, area 5 of the parietal lobe and area 22 of the temporal lobe. From these cortical areas, fibers pass to synapse in the basal ganglions which give off neurons that ultimately reach the anterior horn cells of the cord. These basal ganglions are composed of four deeply placed masses of gray matter, the caudate, lenticular and amygdaloid nuclei and the claustrum. The caudate and lenticular nuclei, together with the internal capsule which separates them, constitute the corpus striatum.

The function of the pyramidal and extrapyramidal tracts is to act in unison in the performance of voluntary movement. The extrapyramidal fibers have to do with movement as a whole and exert an influence in bringing about synergic movement. The pyramidal tracts are more concerned with the carrying out of finely specialized movements.

Clinical study indicates there are three fairly distinct syndromes which may be ascribed to lesions of the striate body. The most pronounced symptoms are (1) changes in muscle tone; (2) the appearance of a peculiar type of tremor; (3) the development of certain choreiform and athetoid movements, and (4) the suppression of or conspicuous alteration in the performance of normal automatic associated movements.

In lesions of the globus pallidus, there are (1) the development of increased muscle tone throughout the entire body, with the production of the characteristic attitude and facies of paralysis agitans; (2) suppression of the normal automatic associated movements, and (3) the appearance of tremor characterized by its occurrence during rest but its increase on exertion or excitement.

The second syndrome involves the lenticular nucleus and results in (1) hypertonicity of the muscles; (2) tremor which is regular, rhythmic and increased by excitement, attention and voluntary effort, and (3) dysarthria and dysphagia.

This syndrome is typified by Wilson's disease, or progressive lenticular degeneration.

A third syndrome is that of the corpus striatum in which the caudate and lenticular nuclei are both affected. Here the symptoms are (1) muscular spasms producing athetoid and choreoathetoid movements; (2) rhythmic oscillation in the limbs constituting a fine tremor; (3) exaggeration of automatic associated movements, and (4) spasmodic outbursts of laughing and crying.

The diagnosis of an encephalobulbospinal type of poliomyelitis was made.

SUMMARY

In this patient the bulbar symptoms, dysarthria and dysphagia, the fluids coming through the nose, retention of urine in the bladder with overflow dribbling, obstinate constipation, somatic quasisegmental involvement of the peripheral muscles, a count of 50 cells in spinal fluid obtained by lumbar puncture, the history of exposure in an epidemic area (Minneapolis), the results of the neutralization test and the fact that the patient had recovered from his tremors, all lead to diagnosis of the condition as poliomyelitis.

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SPONTANEOUS PLEURAL EFFUSION IN A NEWBORN INFANT

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AND
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A REVIEW of the American literature of the last forty years has revealed only 10 cases of primary pleural effusion in infants under 1 year of age. All 10 cases were reported as spontaneous chylothorax. The case reported here is the only known one of primary pleural effusion in a newborn infant in which the effusion was nonchylous.

REPORT OF A CASE

E. W. was born on Sept. 16, 1947, at the Bronx Hospital by normal spontaneous delivery. The child breathed and cried spontaneously. A physical examination fifteen hours after birth revealed no abnormalities other than severe substernal retraction on inspiration and some dulness over the right side of the chest compared with the left. A roentgenogram of the chest (fig. 1*A*) was made on the second day of life. There was a shadow in the right side of the chest due to a moderate-sized pleural effusion surrounding the lung from base to apex. This was verified by the appearance of the roentgenogram made after aspiration. Thoracentesis on the second day of life yielded 75 cc. of a turbid orange fluid. Air was injected to outline the structures within the chest. A second roentgenogram (fig. 1*B*) showed a shift of the mediastinum to the left, absence of most of the fluid and a pneumothorax on the right side. A total of 5 chest taps was performed at about five day intervals. Each time between 60 and 110 cc. of a dark orange fluid was removed from the right side of the chest. Repeated roentgenograms of the chest showed the presence of fluid prior to the chest taps, its absence directly following the tap and reaccumulation within a few days. However, after the last tap on the twenty-seventh day of life a roentgenogram of the chest showed disappearance of the fluid, and by the thirty-fifth day of life another roentgenogram of the chest showed only moderate pleural thickening on the right. By the forty-second day of life there was no roentgenographic evidence of fluid in the chest.

At the time the first chest tap was performed, the possibility of a chylous effusion was considered, although the orange color of the fluid rendered this unlikely. The laboratory reported the presence of bile in the first specimen, but repeated subsequent examinations were negative for bile. There was no ether-soluble material in any specimen. Considerable mucoprotein was reported. Cellular elements present were small lymphocytes, plasma cells, neutrophils, eosinophils and some large cells with single and double nuclei. Smear and culture revealed no organism. No acid-fast bacilli could be demonstrated and guinea pig inoculations gave negative reactions after six weeks.

The possibilities of an abnormal communication between the trachea and the esophagus and of an obstruction in the bronchi were considered. A barium sulfate swallow on the eighteenth day of life revealed nothing abnormal. Bronchoscopy

on the seventeenth day of life showed the right main bronchus to be slightly smaller than the left. No obstruction was seen.

At birth the child weighed 7 pounds 4 ounces (3,288.5 Gm.). He maintained his weight for three weeks and then gained weight rapidly on an evaporated milk

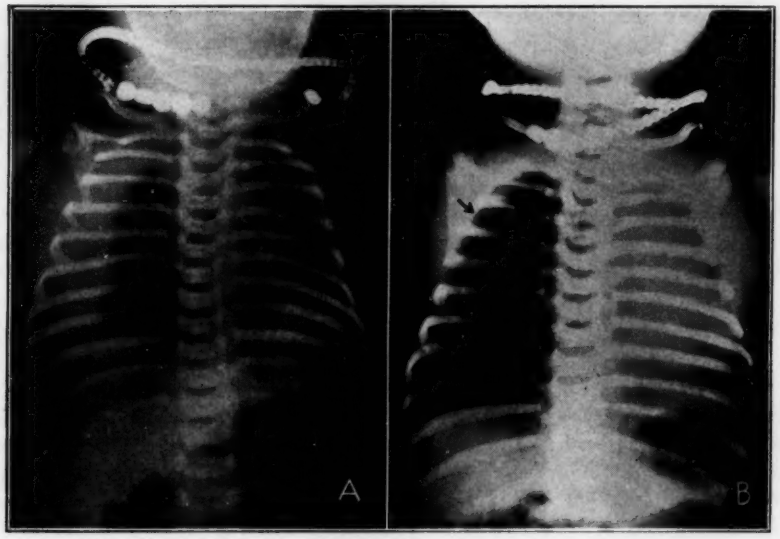

Fig. 1.—Roentgenograms made on second day of life: *A* shows pleural effusion on right side; *B*, the appearance after thoracentesis and injection of air. Partial pneumothorax on right side.

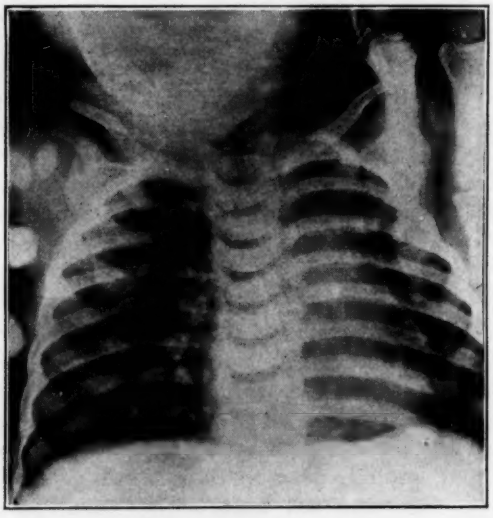

Fig. 2.—Roentgenogram made at 3 months of age. Right side of chest is normal.

formula up to the time he was discharged from the hospital at 6 weeks of age, weighing 8 pounds 9 ounces (3,883.9 Gm.). During the infant's stay in the hospital his temperature was always normal except for two isolated rises to 100 F.

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The patient was readmitted to Bronx Hospital at 3 months of age for follow-up study. His weight had increased to 10 pounds 8 ounces (4,762.7 Gm.) on an evaporated milk formula. His mother had noticed no abnormalities about the child's respirations. Results of physical examination were normal except for occasional sternal retraction on inspiration. A roentgenogram of the chest (fig. 2) showed atelectasis of the upper lobe of the left lung. Repeat bronchoscopy revealed secretions in the trachea and bronchi. Iodized oil U. S. P. was instilled and bronchography showed good filling into the region of the lower lobe of the left lung and partial filling into the midportion of the right lung.

COMMENT

Von Reuss,[1] Finkelstein [2] and Brennemann [3] stated that pleural effusion in newborn infants is rare. Von Reuss [1] stated that it is seen only as a rare complication of pneumonia, tuberculosis and rheumatic infection, but he gave no case references. Finkelstein [2] observed 4 cases of serous pleural effusion in infants between the ages of 7 and 14 months, but all were secondary to pneumonia. Brennemann [3] stated, "Serous pleurisy is a relatively rare condition in childhood. It is rarely, if ever, a primary condition."

One can only speculate as to the causation of the pleural effusion in this child. Infection was not a factor, inasmuch as the child was practically afebrile and repeated smears, cultures and guinea pig inoculations of fluid from the chest revealed no organism. There was no evidence of infection in the mother prior to delivery.

Two remote possibilities may be considered: (1) traumatic pleurisy with effusion and (2) a concealed pneumothorax with effusion. Everhart and Jacobs,[4] in their report on a 15 day old infant with chylothorax, postulated that the cause of the effusion was trauma to which the patient was subjected following delivery. Their patient was delivered at home after a fourteen and a half hour labor with a coil of cord wrapped tightly around the neck—a common type of delivery with an exceedingly unusual complication.

With regard to the second possibility, the large effusion seen on the first roentgenogram could easily conceal a small amount of air in the pleural cavity, especially when one realizes that the only initial film was taken with the patient in a horizontal position. In this position any air that might be present would rise to the superior portion of the pleural cavity and be concealed by the dense shadow of the dependent fluid. De Costa [5] collected 69 cases of pneumothorax occurring in the first few months of life. He listed the causes of spontaneous pneumothorax in the newborn as follows:

1. Congenital anomalies, such as pulmonary fistulas, and abnormalities of the pulmonary vessels.

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1. Von Reuss, A. R.: The Diseases of the Newborn, New York, William Wood & Company, 1922.

2. Finkelstein, H.: Lehrbuch der Säuglingskrankheiten, ed. 2, Berlin, Julius Springer, 1921.

3. Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. 2, chap. 53, p. 3.

4. Everhart, J. K., and Jacobs, A. H.: Chylothorax: Review of the Literature and Report of Case in Newborn Infant, J. Pediat. **15**:558-562 (Oct.) 1939.

5. De Costa, E. J.: Spontaneous Pneumothorax of the Newborn, Am. J. Obst. & Gynec. **39**:578-592 (April) 1940.

2. Inflammatory processes associated with small pulmonary abscesses, from either pneumonia or septic emboli.

3. Trauma, including fractured clavicle, fractured rib, direct parenchymatous injury and cough.

4. Mechanical obstructions, such as mucus, vernix or meconium blocking the air passages, cord around the neck, struma or enlarged thymus.

5. Artificial respiration.

If the history and roentgenographic, laboratory and bronchoscopic findings of this case are considered, it is seen that none of De Costa's [5] causes are applicable. The first roentgenogram was taken approximately thirty hours after birth. If we assume that the effusion was secondary to a pneumothorax, then thirty hours is an exceedingly brief period to permit the accumulation of an effusion in excess of 75 cc. Moreover, De Costa [5] made no mention of pleural effusion in his discussion of 69 cases of pneumothorax in infancy. Labate [6] analyzed 1,114 fetal and neonatal deaths over a ten year period at Bellevue Hospital in New York city. Eight hundred and sixty-eight postmortem examinations were performed. Although pulmonary lesions were the second largest cause of death, no mention was made of pleural effusion with or without pneumothorax.

CONCLUSION

An unusual case of primary pleural effusion in a newborn infant is presented. Possible etiologic factors are considered.

Dr. Harry Wessler, director of medicine, and Dr. Joseph Lapin, attending pediatrician, of Bronx Hospital, assisted in the preparation of this case report.

Albany Hospital, New Scotland Avenue (Dr. Cugell).

6. Labate, J. S.: A Study of the Causes of Fetal and Neonatal Mortality on the Obstetric Service of Bellevue Hospital, Am. J. Obst. & Gynec. **54**:188-200 (Aug.) 1947.

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Progress in Pediatrics

MONGOLISM IN ONE OF TWINS AND IN ANOTHER SIBLING

Report of a Case

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BUFFALO

MONGOLISM is a congenital anomaly of unknown etiology. Attempts to attribute it to any single cause or to a combination of etiologic factors have failed. One main reason is that no experimental approach to the subject has been possible because the condition is recognized only in man. As a rule, mongolism occurs sporadically in family pedigrees, as well as among siblings; this circumstance indicates that the factor, or the combination of factors, which leads to this entity occurs only rarely. Therefore, cases of repeated incidence in a family have always aroused great interest and have been looked on as experiments of nature of possible value in contributing to an eventual understanding of mongolism.

Up to the present, forty-eight families have been reported in which mongolism occurred more than once among siblings. The data are exclusive of those pertaining to families in which there were 2 mongoloid children who constituted a set of affected twins. From the literature I have culled two families, each having 4 mongoloid siblings, and four families, each having 3 mongoloid siblings, while the remaining forty-two have 2 such children per family.

The occurrence of mongolism in one or both of twins also constitutes an event which has greatly interested students of the subject. I have collected from the literature data on 101 sets of twins in which one or both members were affected.

At the Children's Hospital, Cincinnati, a family was observed in which the birth of a mongoloid child was followed by the birth of twins, one of whom was mongoloid. To my knowledge, only one similar incident has been described previously, that by Penrose (1934 *b*), although the case reported by van der Bogert (1916) has been cited in the literature many times as an example of a family in which the birth of a mongoloid child was followed by that of twins, one of whom was stated to be mongoloid also. However, van der Bogert, himself, did not consider the twin a true mongolian imbecile but rather a syphilitic

From the Children's Hospital Research Foundation, Department of Pediatrics, University of Cincinnati College of Medicine.

child who had been mistaken previously for a mongoloid child. He described him as "much brighter than his normal twin brother" and as showing "dwarfism" but "none of the mongolian hand stigmata." The case presented here is, therefore, the second one of its kind in which in one family there were 2 mongoloid children, one of them a twin.

TABLE 1.—*Multiple Cases of Mongolism in Siblings of the Same Family**

Author	Year	Comment
Four mongoloids in one family		
Babonneix and Villette	1916	
Péhu and Gaté	1937	
Three mongoloids in one family		
Herrman	1917	
van der Scheer	1919	A sister of these 3 had a mongoloid child
Malkin	1928	Cited by Macklin (1929)
Bixby	1939	Cited by Benda, case 2 (1946)
Two mongoloids in one family		
Brudzinski	1907	Also reported by Leuckowiz (cited by Brousseau, 1928)
Shuttleworth	1909	
Stevens	1915	
Herrman	1917	Two families
van der Scheer	1919	Two families
Pardee	1920	Also reported by Glassburg (1924)
Cozzolino	1921	Two families
de Biehler	1922	
Husler	1923	
Ibrahim	1923	
Scott	1923	
Rietschel	1925	Cited by Orel (1926)
Dietrich and Berkley	1926	
Reuben and Klein	1926	
Borovsky	1928	
Mackintosh	1928	
Brousseau	1928	Two families
Sedgewick	1928	From Brousseau (1928)
Bingenheimer	1933	
Penrose	1934(b)	One a twin
Malvasi	1935	Two families; cited by Jervis (1942)
Johnson	1936	Two families; cited by Jervis (1942)
Lahdensuu	1937(a)	
Lahdensuu	1937(b)	Half-sibs by different fathers
Tataflore	1937	
Sirkin (American Indians)	1937	Half-sibs by different fathers
Chevrel-Bodin and others	1938	
Doxiades and Portius	1938	
Illing	1939	Three families
Schröder	1940	Two families; cited by Jervis (1942)
Halperin	1940	
Benda	1946	
Auden	1947	

* Authenticated cases or those which have found generalized acceptance only are included in tables 1 and 2. Of the cases in this table 2 are of special interest, those of Lahdensuu (*b*) and Sirkin. Each mother, after having a series of normal children, had 2 successive children with mongolism by different fathers.

FAMILY HISTORY

The pedigree of the family shows no consanguinity; the occurrence of mental deficiency or mongolism (except in the propositi) was denied. There was no other twinning in the immediate family, although the mother stated that her great, great-grandmother had a twin sister. The father, born in 1910, was alive but in questionable health. He was discharged from the armed services with a diagnosis of psychoneurosis.

The mother, born in 1907, had always been of slight build, easily upset and extremely nervous. For this nervousness and because of the presence of a goiter, which was not apparent to her, her thyroid was removed in 1935 shortly

TABLE 2.—*Mongolism in Twins; List of Pairs of Twins in Which One or Both Are Mongoloids*

I. Unliked sexed twins—one affected
18 Cases *

Neumann, cited by Halbertsma (1923)	1899
Hultgren	1915
Cassel, cited by Halbertsma (1923)	1917
Swanberg and Haynes, cited by Halbertsma (1923)	1919
McLean	1922
Halbertsma (cases 3 and 4)	1923
Krabbe (case 4)	1926
Orel (case B)	1926
Comby (case 22)	1927
Armstrong	1928
Bauer	1930
Halbertsma, cited by Orel	1931
Rosanoff and Handy (cases 3, 4 and 5)	1934
Blechmann	1936
Lahdensuu	1937

12 Cases †

Shuttleworth (also reported by Wood in Australia, 1881)	1909
Comby (case 65)	1917
Cassel, cited by Halbertsma (1923)	1917
Pelper	1923
Vas, cited by Orel (1926)	1925
Krabbe (case 1)	1926
Shattuck	1929
Waring	1931
Legras, cited by Rosanoff and Handy (1934)	1932
Mouriquand and Schoen	1933
Hellsten	1936
Beidleman	1945

II. Sex not stated—one affected
15 Cases ‡

Fraser and Mitchell	1876-1877
McKee, cited by Swanberg and Haynes (1919)	1908-1909
Halbertsma (case 5, mongoloid boy)	1923
Weigall, cited by Comby (1917)	1923
Cassel, cited by Orel (1926)	1926
Lapage (1 mongoloid and 1 achondroplastic)	1932

Strucovskaja (2 cases)	1932
Doxiades and Portius (5 cases)	1938
Illing (mongoloid boy)	1939
Benda (case 50)	1946

III. Like-sexed twins—one affected
20 Cases §

Kellner, cited by Brousseau (1928)	1913
Clay	1922
Halbertsma (case 1)	1923
Myers	1925
Mitchell and Downing	1926
Dietrich and Berkley	1926
Krabbe (case 5)	1926
Chown	1927
Brousseau (Brainerd)	1928
Orel (case P)	1931
Legras	1932
Adalid and Escardó	1932
Hopwood	1932
Penrose	1934 (b)
Mattioli-Foggia, cited by Jervis (1942)	1936
Hellsten	1936
Sherman and Tjaden	1938
Peluffo, cited by Jervis (1942)	1938
Illing	1939
Schröder, cited by Jervis (1942)	1940

17 Cases

Halbertsma (case 2)	1923
Siegert, cited by Orel (1926)	1923
Moro, cited by Orel (1926)	1923
Jewesbury (case 10)	1925
Orel (case BE)	1926
Wieland, cited by Orel (1931)	1926
Krabbe (case 4)	1926
Gautier and Coeytaux	1926
Dietrich and Berkley	1926
Coupland, cited by Greig (1927)	1927
Petzoldt	1930
Orel (case F)	1931
Pantagna	1931
Rosanoff and Handy (case 2)	1934
Sherman and Tjaden	1938
Southwick	1939
Warner (typical mongol, twin not seen but reported entirely normal)	1947

IV. Like sexed twins—both affected
8 Cases ¶

M **	de Bruin	1902
?	Strauch	1923
M	Reuben and Klein (Rosanoff and Handy, case 9)	1926
M	Dickey	1927
M	Blechmann and others	1932
?	Penrose	1934
D	MacKaye	1936
D	Jervis	1942

10 Cases #

M	Hjorth, cited by Shuttleworth, Krabbe (cases 2 and 3) and Rosanoff and Handy (case 8)	1906
M	Brückner	1926
?	Stransky (case 7), cited by Rosanoff and Handy (1934)	1930
M	Bauer	1930
?	Russell	1933
M	Lund	1933
?	Rosanoff and Handy (case 1)	1934
D	Gordon and Roberts (both were also paraplegic)	1938
M	Tobler	1938
M	Ford and Frumkin	1942

V. Sex not stated—both affected ††
2 Cases

Fanconi	1939
Ingalls	1947

* Twins in which boy was mongoloid and girl unaffected.
† Twins in which girl was mongoloid and boy unaffected.
‡ Twins of undetermined sex, one child of whom was affected.
§ Twin boys of whom one was affected.
‖ Twin girls of whom one was affected.
¶ Twin boys both of whom were affected.
# Twin girls both of whom were affected.
** M signifies identical (monozygotic) twins in the author's opinion. D indicates non-identical (dizygotic) twins and the question mark, those whose identity was questionable or not discussed.
†† Twins of undetermined sex, both of whom were affected.

after her marriage. No definite signs or symptoms of hyperthyroidism (other than nervousness) could be elicited from the history. However, she felt better and less nervous following thyroidectomy. She appeared tired, distraught and older than her stated 40 years, but it must be remembered that she carried the burden of care of 4 children, 3 of them small and helpless and 2 of these with mongolism.

The mother's first pregnancy, which terminated in January 1937, resulted in like-sexed twins; because of a single placenta they were considered identical. They were free of gross abnormalities. The first twin was "large" but survived only a few hours; the second was greatly underdeveloped and was born dead. No records are available.

The second pregnancy resulted, in August 1938, in the birth of a normal girl who died of pneumonia at the age of 5 months.

The third pregnancy terminated, in April 1940, in the birth of William Frederick, a normal boy, of spare and wiry frame and adequate intelligence. He was quite responsible in caring for his younger siblings and did well in school. Physical examination revealed no abnormalities.

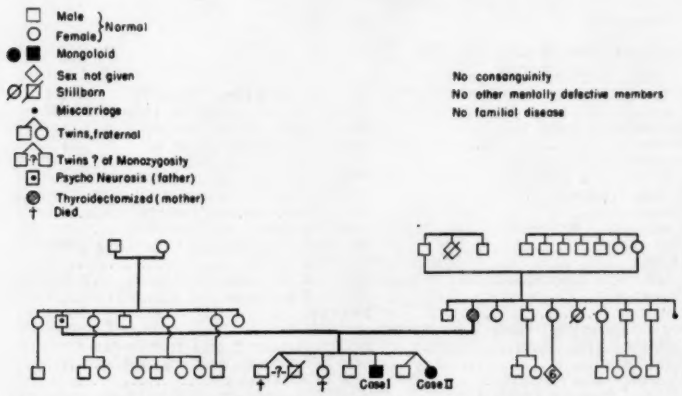

Fig. 1.—Chart showing pedigree of family.

The fourth pregnancy was characterized by extreme nervousness on the part of the mother. She felt "weakened" and "had to lie down all the time." She found herself unable to keep up and about or to do her housework and stayed in bed for a large portion of the nine months. She felt "worse" during this pregnancy than during any of the others and "broke into tears at the slightest provocation." Her own description of this condition recalled that which Comby (1917) observed in a large proportion of mothers of mongoloid children and which he considered typical.

The result of this fourth pregnancy was Fred William (case 1) who was born March 1945 at full term, weighing 8 pounds (3,628.7 Gm.). His mother believed he was a "blue baby." She recalled that he refused his feedings for the first few days, was limp and "like dead." She was told soon after his birth that he would develop slowly. He was never breast fed and could take nourishment only when supine. His development was indeed slow, and he took his feedings poorly throughout the first year of life. Then, after one year he began to accept the bottle well but could not use a spoon or cup. He did not sit up before 12 or 14 months of age.

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When first seen at the clinic at the age of 15 months, he was recognized as a typical mongoloid child. He had a flat and brachycephalic head, slanted eyes with prominent epicanthic folds (fig. 2) and large rolls of fatty tissue at the nape of the neck and over the dorsa of the hands and feet. The nipples were completely flat and very small. He played constantly with his protruding tongue. Hyperextension of all the joints and complete hypotonia were noted. The hands were typically spadelike with short, incurved little fingers. The ears were low set, square and unequal. No cardiac murmur or other evidence of a lesion of

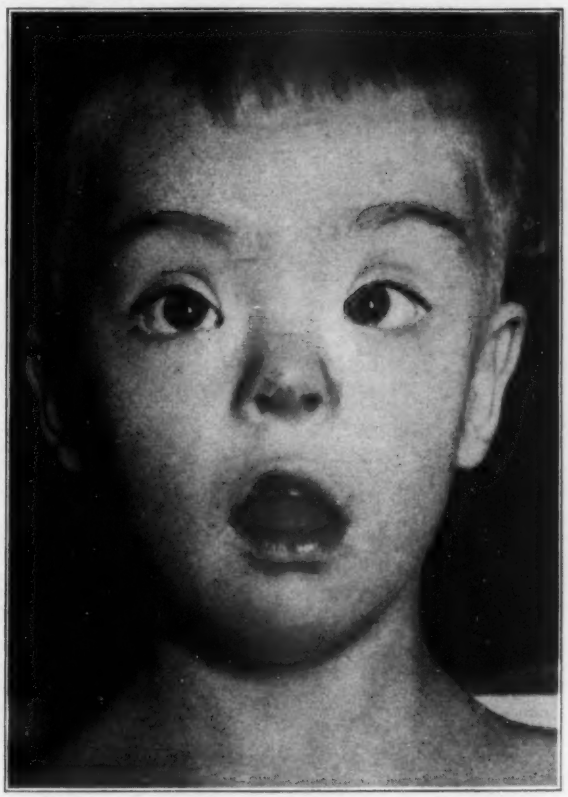

Fig. 2 (case 1).—Mongoloid boy at the age of 15 months. Note flat, brachycephalic head and slanted eyes with prominent epicanthic folds.

the heart could be detected. The child was usually content; he whined occasionally but almost never cried. He could sit up "tailor fashion" but made only weak and infrequent attempts to crawl and no attempt to stand or walk.

When seen again at the age of 2 years, he crawled and stood with aid but not alone and made no attempt to walk. He was given ¼ to 1 grain (0.015 to 0.06 Gm.) of thyroid daily, and, after six months of treatment, improvement was reported by the mother; the child could walk alone and feed himself with a spoon. His appetite improved greatly and, according to the mother, he was

generally much brighter and more advanced. None of the stigmas have been altered, however, and the child remains decidedly hypotonic and retarded mentally.[1]

The mother's fifth pregnancy was normal and happy throughout and resulted in twins, Eugene and Mary Jean, who were born in October 1946 at the Cincinnati General Hospital. The first born, a boy, was entirely normal, weighing 7 pounds, 3 ounces (3,260.2 Gm.). The second twin, a girl weighing 6 pounds 14 ounces (3,118.5 Gm.), was immediately recognized as mongoloid (case 2).

When first seen in the clinic in March 1947, the twins showed a decided difference in development. Eugene weighed 17 pounds 11 ounces (8,022.9 Gm.)

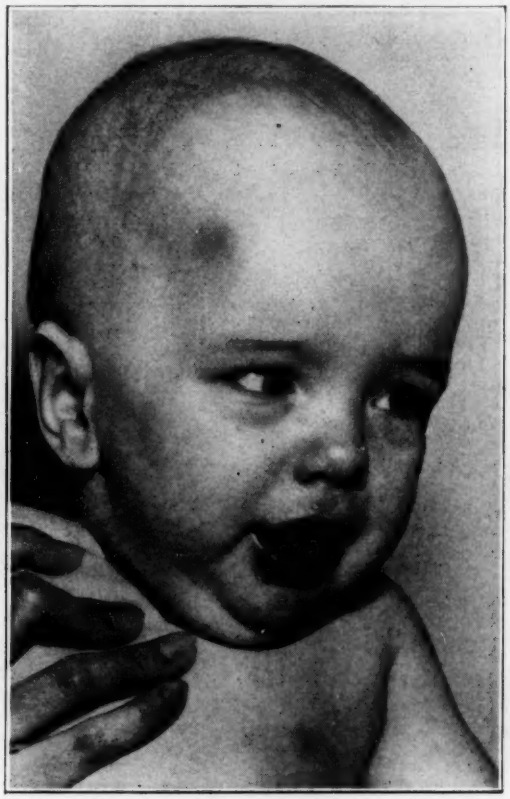

Fig. 3.—Normal fraternal twin of mongoloid girl (case 2).

and measured 28 inches (71 cm.), being 3 pounds (1,360.8 Gm.) heavier and 3¾ inches (9.5 cm.) taller than his twin. His stage of development was adequate for 6 months of age. He could not sit up alone but could maintain himself in a sitting position. He had been vocalizing for a month, and he laughed aloud and smiled when talked to. He grasped at objects and appeared alert, always trying to pull himself up to an erect position. Physical examination revealed that he was entirely normal and showed none of the stigmas of mongolism (fig. 3).

1. This child subsequently died of measles in the Cincinnati General Hospital in March 1948.

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Mary Jean was, according to the mother, about one month behind her twin in development. She ate the same amount of food with equal eagerness but weighed only 14 pounds 7¾ ounces (6,570 Gm.) and measured 25¼ inches (64 cm.). She was just commencing to vocalize and had not learned to laugh. She made no attempts to sit or pull herself erect and flopped over limply when placed upright.

She was typically mongoloid with flat and brachycephalic head, epicanthic folds, slanting eyes (fig. 4, left), high-arched palate, large protruding tongue and excessive rolls of fat on the nape of the neck (fig. 4, right) and on the dorsa of the hands and feet. The ears were square and unequally low set. The hands were spadelike with low take off of the thumb and short, incurved little fingers. The nipples were flat and poorly developed and the vulva, large and puffy. This child, like her mongoloid brother, failed to show signs of a cardiac lesion or notable herniation of the umbilicus.

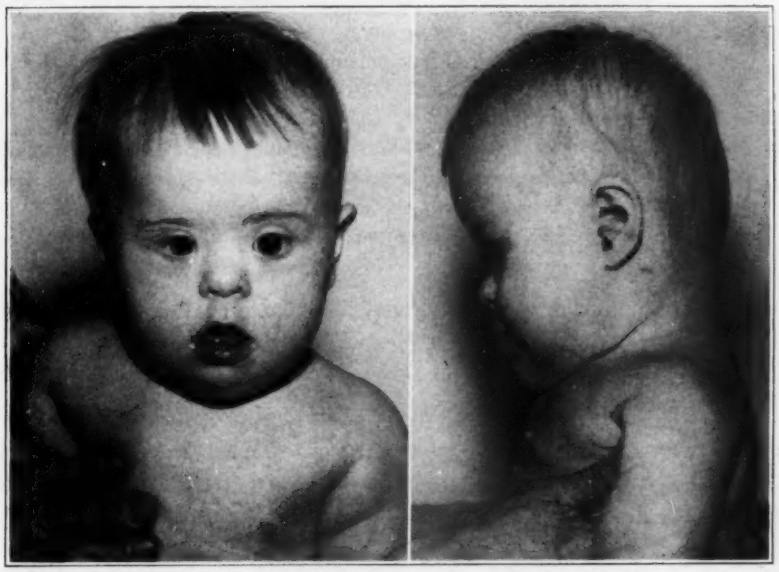

Fig. 4 (case 2).—Photograph on left shows flat, brachycephalic head, epicanthic folds and slanting eyes. The right view shows rolls of fat on nape of neck and square ear.

After six months, on a follow-up examination in the clinic, further discrepancy could be noted in the development of the twins. At 1 year, the normal boy was very active and crawled across the room; he could walk when holding on and spoke several individual words. He was an alert, intelligent-appearing child who screamed for his food when hungry. The girl, in spite of thyroid therapy, could just sit up and made no attempt to crawl. She merely vocalized, speaking no words. She was a content baby who lay drooling and playing with her protruded tongue; she rarely cried and weighed only 20 pounds 2 ounces (9,128.5 Gm.), compared with the 30¼ pounds (13,721.2 Gm.) of her twin. She was subject to frequent colds. The mother felt that, although far behind her twin, she was developing at a faster rate than did her older mongoloid brother

COMMENT

It is generally accepted that maternal age plays a role in the causation of mongolism, although few authors agree on the extent or mode of action of this factor. Bleyer (1938) reviewed the material of many authors and compiled massive statistics on the role of maternal age. His conclusions coincided with those of Jenkins (1933) and Penrose (1932 *a*). He stated:

> The peak maternal age in the general population in this country in the year 1934 [from 2,000,000 births] was 24; the peak age of the mothers producing mongoloid imbeciles in this series of 2,822 cases was 41.
>
> The incidence of mongolism increases steadily through the child-bearing period, being lowest at the beginning and highest at the end, the likelihood of producing a mongoloid imbecile increasing in direct proportion to the number of menstrual cycles through which a woman has passed. [See Jenkins' statement concerning logarithmic, not direct proportion, page.]
>
> By comparing the number of mongoloid imbeciles born in each quinquennium of maternal age with the number of children born to mothers of similar age groups in the general population, it was found . . . that in the [fifth] quinquennium (35 to 39 years), as normal fecundity declines, the percentage of births of children with mongolism as compared with the percentage of births of normal children rises prodigiously, to 25:1, showing a definite predisposition to mongolism. . . . The succeeding five year period (40 to 44 years) shows a further increase to 75: 1.

The factor of maternal age may have played a role in the family presented here, in which the mother gave birth in two successive pregnancies to 2 mongoloid children at the ages of 38 and 40 years, respectively.

Many authors have considered the endocrine status of the mother as of maximum importance in the production of mongoloid infants. One of the most recent and ardent proponents of this theory is Benda (1946) who, in a review of the literature, states:

> The inability to become pregnant, constitutional abortions, continuation of menstruation, and the fact that attempted abortions (9.3 per cent) seem of some importance indicate that not the ovum itself but the endocrine environment of the ovum is at fault . . . one cannot fail to notice the high percentage of cases in which thyroid deficiency and goiter of the mother was found. . . . All the hormones are kept in delicate balance and if one is too powerful or another too weak, the balance is disturbed and bleeding and abortion occur. . . . We have seen that mongolism occurs under the same conditions as abortion, threatened abortion, prematurity and hormonal sterility. We have further seen that these are indications of thyroid and pituitary deficiency. Although the exact mechanism of deficiency resulting in congenital acromicria of the baby is still a matter of speculation, the facts at hand are sufficient to narrow the possible causes to a small number of factors.

The mother of the children reported here had had a thyroidectomy. From this, one might conclude that she had an endocrine imbalance

either prior to or after her operation, and the circumstances could be interpreted as favoring the theory of maternal endocrine imbalance.

A different idea was presented by Halbertsma who, as early as 1923, directed attention to the fact that mongolism may occur in only one of twins and that such twins were always believed to be the product of a two egg pregnancy (nonidentical twins). Cases of mongolism in both twins of different sex are unknown even at present, but cases have been described in which both like-sexed twins were affected. Halbertsma drew the conclusion that mongolism is not acquired by the fetus but is germinal in origin. A similar view was held by Macklin (1929) who, from a survey of the literature, came to the conclusion that environmental influences "are not the cause of mongolian idiocy, but that it is due to inherited defects, and so is germinal in origin." She considered the mode of origin to be complex and suggested "that the disease is due to the simultaneous presence in the germ cell of 5 pairs of recessive or 2 dominant and 4 recessive factors carried in as many chromosomes." However, such outstanding geneticists as Penrose (1932*a*) and Haldane (1937) were of the opinion that, in addition to genetic factors, extrinsic circumstances contribute to the causation of mongolism; Penrose stated: "Attempts, however, to describe the results on straightforward mendelian hypotheses have so far been either vague or manifestly incorrect."

In the present family of 7 children 2 were mongoloid. The mongoloid twin differed in sex from her twin. These facts are compatible with the assumption that mongolism is of germinal origin.

Recently, Ingalls (1947) has emphasized that mongolism is determined at about the eighth week of gestation, a period which is relatively late in embryonic life:

> While the causative agents of mongolism are relatively numerous, the causative mechanisms are few in number and operate about the eighth week of fetal life. Causative agents include hemorrhage, threatened abortion, pathologic abnormalities of the uterus and cerain acute intercurrent infections [rubella]. Experimental and clinical evidence suggests that lack of oxygen to the fetus may be an important mechanism, with temporary starvation and the accumulation of toxic metabolites to be evaluated.

In the family reported on here one might possibly consider as abnormal the first of the pregnancies which resulted in a mongoloid child, since the mother felt exhausted and depressed throughout gestation. But in the second pregnancy which resulted in twins, one of whom had mongolism, there was little evidence of any abnormality or interference by the agents or mechanisms suspected by Ingalls.

Many students of mongolism have considered theories of cytoplasmic injury to the ova. Prominent among these authors are Geyer (1939), Jenkins (1933) and Rosanoff and Handy (1934). Geyer considered

anomalies of the ovum as primarily responsible. Jenkins concluded that "mongolism is due to diminished viability of the ova." He wondered why the incidence of mongolian idiots behaves as a logarithmic function in mothers past 32 years of age and why the function breaks below this age. He introduced the concept that

> . . . in the population of ova there is continually a certain mortality rate. In a period between that of complete viability and failure of reproductive function ova pass through a mongolian-genetic stage.

He explained further:

> In view of the relative infrequency of mongolism it would be unlikely that the two ova producing dizygotic twins should be in this stage. On the other hand, monozygotic twins arising from a single ovum must necessarily both be mongolian idiots if affected at all. One would expect the occurrence of mongolism in more than one member of a sibship to be relatively uncommon and yet to occur with a little higher frequency than purely chance factors would explain. . . . As the age of the mother increases the fertility is known to diminish. This diminution in fertility may be reasonably ascribed to a diminished reproductive viability of the ova. One would, therefore, expect an increasing incidence of mongolism among the children of women of advancing age.

He concluded that:

> The hypothesis that mongolism is due to a diminished viability of the ovum, short of complete failure of development, makes it possible to harmonize the superficially paradoxical evidence pointing toward the germ cell and maternal age as etiologic factors.

Rosanoff and Handy presented another aspect of this theory when they stated that:

> All the known facts concerning mongolism seem to point to some condition in the ovary as underlying its pathogenesis. . . .
>
> We have, however, a sufficient amount of circumstantial evidence . . . to justify the speculation that *foci of tissue change—perhaps scars—marking the sites of old ovulation are the cause of the trouble.*
>
> Accordingly, the ovaries of any girl who has menstruated one or more times contain one or more foci at which injury to an ovum may occur such as to lead to mongolism.
>
> By this theory, the chance of producing a child with mongolism increases with the passing of each menstrual period—which, of course, harmonizes with the correlation of the incidence with the age of the mother.

Since in the present case neither the uterine mucosa nor the ovaries of the mother were available for pathologic examination, there is no evidence for either proof or disproof of these theories of damage to the ovum. Similar speculations involving the ovaries and tubes have been advanced by Southwick (1939). Schachter (1936) blamed the condition of the uterine mucosa following curettage, and Mayerhofer (1939) was of the opinion that the answer lay in the ill effects on the uterine mucosa of recent pregnancy or of a long series of pregnancies.

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The mother of the present patients produced children with mongolism in her fourth and fifth pregnancies, which were separated by only ten months, so that these facts fit in well with the theory of damage to the maternal reproductive tract.

Obviously, there are good arguments against, as well as for, each of these theories and there are certain easily detectable flaws in all of them. However, it is not within the scope of this paper to attack these theories or even to point out their inaccuracies. On the other hand, it is of interest that the circumstances surrounding the case reported here are compatible with all these theories, indicating that they are too general and comprehensive and not specific enough.

Actually, most of these theories do not contradict but rather supplement each other. Endocrine changes and disturbances, decreased viability and reproductive ability of the ova and scarring of the ovaries or of the uterine mucosa could be related to advancing age and to a greater number of past menstrual periods. All these, as well as infection or trauma, individually or in combination, may be necessary to bring out a genetic factor. Haldane (1937), citing the work of Penrose (1932 *a*), suggested that an unfavorable condition associated with maternal age, as well as genetic factors, is concerned in the determination of mongolism. He compared the causation of mongolism with that of polydactylism in four strains of inbred guinea pigs studied by Wright (1926). This investigator proved that the predominant but not the sole factor in determining the incidence of polydactylism was maternal age, and that this incidence varied both with the mother's age and the genetic constitution of the group.

Rosanoff and Handy (1934) in their paper made a plea for

> . . . a systematic pathologic investigation of the ovaries of women who have given birth to mongolian idiots—whenever an opportunity for doing so might present itself.

This, in their opinion, may eventually "throw some light on the matter." I join them wholeheartedly in this plea and suggest that a careful study of serially sectioned ovaries of the mother of the present and similar patients be made, since such studies could prove of inestimable value toward the solution of the problem. For, while all these explanations have their merits, the decisive factor is still unknown. In spite of all the theories advanced to date, one is still unable to predict or prevent the occurrence of mongolism.

SUMMARY

Cases of 2 or more mongoloid siblings in the same family are tabulated. Cases of mongoloid twins from the literature are tabulated and

a new case added. A case history of a family is presented in which 2 siblings were mongoloid—one being a twin.

Several of the theories of the causation of mongolism are considered and are found to be compatible with the circumstances in the case presented.

The true etiologic factor, or combination of factors, causing mongolism remains obscure.

333 Linwood Avenue (9).

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COMPOSITION OF HUMAN COLOSTRUM AND MILK

ICIE G. MACY, Ph.D., Sc.D.
DETROIT

WITH the information available, the obvious approach to the problem of infant feeding is based on the use of human milk when feasible and of formulas simulating it as nearly as possible when for any reason breast milk cannot be made available to an infant. With knowledge of the chemical composition of colostrum and human milk as a pattern, corresponding formulas can be prepared to meet the requirements for growth and development of both premature and full term infants. A report by the Subcommittee of the Committee on Maternal and Child Feeding, of the Food and Nutrition Board of the National Research Council,[1] which considered the advantages of breast milk as a specific food for infants, the advantages of breast feeding as a technic in child care and the objections and contraindications to breast feeding, stated:

> As a food, human milk still remains the best type of milk for young infants, although it probably is not always a complete food after the first few weeks. Breast milk has definite preventive and therapeutic value. It is economical, automatically produced and timesaving in the household. By and large, the country over, breast milk is the safest food for premature babies who are mature enough to suckle at the breast. The younger ones may need special nutritional and other facilities.

At the turn of the century, the quantitative composition of human milk could be described in terms of only about a dozen components. In stark contrast, today, approximately one hundred components are known always to be present in human milk in varying quantities and proportions. The limited knowledge prevailing formerly was based on analyses of samples of milk collected from heterogeneous groups of lactating women, usually wetnurses, under a variety of uncontrolled conditions, which since have been demonstrated to affect the composition of milk, and analyzed by less reliable chemical procedures than are available today. If human milk is to serve as the pattern of nutriments generally best suited for infants, precise knowledge of its composition acquires new significance at present when the United States is faced

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From the Research Laboratory, Children's Fund of Michigan.

1. Aldrich, C. A.: The Advisability of Breast Feeding: A Survey of the Subcommittee of the Committee on Maternal and Child Feeding, National Research Council, J. A. M. A. **135**:915-916 (Dec. 6) 1947.

with a decline in breast feeding and an ever growing list of infant foods advertised widely by the press and radio for compounding formulas to be used as substitutes for breast milk and dispensed without medical supervision by drug and grocery stores.

During the past twenty-five years important progress has been achieved in various specialties of medicine and its supporting sciences, especially in physics, chemistry, biochemistry and nutrition. These advances have been responsible for the development of new clinical, mechanical, therapeutic and laboratory procedures, technics, analytic methods and equipment. Further impetus to the accumulation of data pertaining to child bearing and child rearing has come from the enlarging interest of women in problems related to motherhood, an interest which has made them eager to participate in investigations and avid followers of the results, and from closer cooperation of obstetricians, pediatricians, chemists and nutritionists in the application of the new knowledge.

The investigations of the influence of maternal nutrition on infant health and growth carried on during the past twenty years by the Research Laboratory of the Children's Fund of Michigan have included studies of the variability of milk flow and factors promoting or retarding it and of the composition of human milk from the two breasts, at feeding intervals during the day, at intervals in lactation and in relation to intake of nutriments. Observations and analyses from the research have provided values for the composition of human milk which in this report are summarized for the first time. As a composite, they supplement and enlarge the knowledge of the quantity and distribution of the nutriments in the food provided by nature for the growth and development of infants.

METHODS

The difficulties encountered in attempts to combine values from the literature defining the chemical structure of human milk are attributable to discrepancies in age, race, parity and individual nutritional and genetic factors of subjects; in procedures of collection, handling, preservation and analysis of samples; in the intervals considered as periods of secretion of colostrum, transitional milk and mature milk, and in the methods of calculation and presentation of the results. In obtaining the data compiled in this paper, every effort was made to minimize the influence of these factors.

The milk for analysis was manually expressed[2] by highly skilled registered nurses or by the mothers under their direct supervision. At the nursing period immediately preceding a collection any milk remaining in the breasts was expressed and discarded. At the next feeding time the entire volume of milk in the glands was removed. The majority of the samples analyzed represented pooled collections of all the milk in both breasts at each regular nursing time during twenty-

2. Davies, V., and Pratt, J. P.: The Stimulation and Maintenance of Lactation, Am. J. Nursing **46**:242-244 (April) 1946.

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four hours. During the day of collection the composite was accumulated in a covered, sterile container kept in the refrigerator. Special provisions were made for preserving constituents that deteriorated rapidly. The methods and procedures used in the determinations have been described in full in individual publications.[3]

3. (*a*) Barnes, D. J.; Cope, F.; Hunscher, H. A., and Macy, I. G.: Human Milk Studies: XVI. Vitamin D Potency as Influenced by Supplementing the Diet of the Mother During Pregnancy and Lactation with Cow's Milk Fortified with a Concentrate of Cod Liver Oil (A Test on Rachitic Infants and Rats), J. Nutrition **8**:647-657 (Dec.) 1934. (*b*) Beach, E. F.; Bernstein, S. S.; Hoffman, O. D.; Teague, D. M., and Macy, I. G.: Distribution of Nitrogen and Protein Amino Acids in Human and Cow's Milk, J. Biol. Chem. **139**:57-64 (May) 1941. (*c*) Beach, E. F.; Bernstein, S. S., and Macy, I. G.: Intake of Amino Acids by Breast-Milk-Fed Infants and Amino Acid Composition of Cow's Milk and Human Milk, J. Pediat. **19**:190-200 (Aug.) 1941. (*d*) Brown, M.; Macy, I. G.; Nims, B., and Hunscher, H. A.: Human Milk Studies: VIII. A Comparison of the Composition of the Milk from the Two Breasts, Am. J. Dis. Child. **43**:40-51 (Jan.) 1932. (*e*) Coryell, M. N.; Harris, M. E.; Miller, S.; Williams, H. H., and Macy, I. G.: Human Milk Studies: XXII. Nicotinic Acid, Pantothenic Acid and Biotin Contents of Colostrum and Mature Human Milk, ibid. **70**:150-161 (Sept.) 1945. (*f*) Davies, V.: Human Milk Studies: XXI. A Simple Technique for the Manual Expression of Mother's Milk, ibid. **70**:148-149 (Sept.) 1945. (*g*) Davies and Pratt.[2] (*h*) Donelson, E., and Macy, I. G.: Human Milk Studies: XI. Vitamin G (B_2) Content of Mixed Milk, Am. J. Physiol. **100**:420-425 (April) 1932; (*i*) Human Milk Studies: XII. Vitamin B and Vitamin G Content Before and During Maternal Consumption of Yeast, J. Nutrition **7**:231-249 (Feb.) 1934. (*j*) Erickson, B. N.; Gulic, M.; Hunscher, H. A., and Macy, I. G.: Human Milk Studies: XV. The Non-Protein Nitrogen Constituents, J. Biol. Chem. **106**:145-159 (Aug.) 1934. (*k*) Erickson, B. N.; Stoner, N., and Macy, I. G.: Human Milk Studies: XIV. A Critique of the Determination of Nitrogenous Constituents, ibid. **103**:235-248 (Nov.) 1933. (*l*) Lesher, M.; Brody, J. K.; Williams, H. H., and Macy, I. G.: Human Milk Studies: XXVI. Vitamin A and Carotenoid Contents of Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**:182-192 (Sept.) 1945. (*m*) Macy, I. G.; Hunscher, H. A.; Donelson, E., and Nims, B.: Human Milk Flow, ibid. **39**:1186-1204 (June) 1930. (*n*) Macy, I. G.; Nims, B.; Brown, M., and Hunscher, H. A.: Human Milk Studies: VII. Chemical Analysis of Milk Representative of the Entire First and Last Halves of the Nursing Period, ibid. **42**:569-589 (Sept.) 1931. (*o*) Macy, I. G.; Outhouse, J.; Graham, A., and Long, M. L.: Human Milk Studies: II. The Quantitative Estimation of Vitamin A, J. Biol. Chem. **73**:175-188 (May) 1927; (*p*) Human Milk Studies: III. The Quantitative Estimation of Vitamin B, ibid. **73**:189-201 (May) 1927. (*q*) Macy, I. G.; Outhouse, J.; Long, M. L., and Graham, A.: Human Milk Studies: I. Technique Employed in Vitamin Studies, ibid. **73**:153-174 (May) 1927. (*r*) Data to be published. (*s*) Munks, B.; Robinson, A.; Williams, H. H., and Macy, I. G.: Human Milk Studies: XXV. Ascorbic Acid and Dehydroascorbic Acid in Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**:176-181 (Sept.) 1945. (*t*) Nims, B.; Macy, I. G.; Brown, M., and Hunscher, H. A.: Human Milk Studies: IX. Variations in the Composition of Milk at Four Hour Intervals During the Day and Night, ibid. **43**:828-844 (April) 1932. (*u*) Nims, B.; Macy, I. G.; Hunscher, H. A., and Brown, M.: Human Milk Studies: X. Daily and Monthly Variations in Milk Com-

(Footnote continued on next page)

The samples analyzed were obtained from approximately 200 women judged by their physicians to be representative healthy persons from their medical histories, their records during pregnancy and delivery and the health of the infants they were breast feeding. Almost all were multiparas. All the mothers were intelligent and cooperative, and, though socioeconomic circumstances varied greatly, environmental conditions in general were good for all the women and their self-chosen diets ranged from "fair" to "good." Both cross sectional and longitudinal data are included in this compilation, i. e., many of the women provided milk samples at different stages in lactation.

Secretion of Colostrum and Transitional Milk.—The composition of breast milk changes with the establishment and progression of lactation: The concentrations of some constituents increase and those of others decrease as the mammary structures adjust to the demands of milk production. Colostrum, the initial secretion of the mammary glands, is composed of milk products elaborated prior to and following parturition, including whatever cellular constituents and debris remain from the processes of preparation and "flushing out" of the mammary glands and ducts prior to actual emptying of the secreted milk. While the true length of the colostral period is not certain, evidence indicates that it varies with individual women and lasts from one to five days.[4]

The changes in the composition of the secretion from the human breast occur gradually. Values for the second five days post partum provide adequate data for evaluation of the rapidity with which the proportions of chemical constituents characteristic of colostrum are altered to become those of mature milk, although some investigators expressed the belief that the transitional period extends beyond the tenth day post partum and that mature milk does not flow for four to six weeks after delivery. Earlier publications from this laboratory have demonstrated differences in the composition of the milk secreted during the first and second halves of the nursing period,[3r] of the milk obtained from the two breasts [3d] and of the milk secreted at various feeding times during the day.[3t]

RESULTS

From analyses of colostrum, transitional milk and mature milk, values are summarized in tables 1, 2 and 3 for the concentration of total solids, energy, total fat, total protein, casein, whey protein, albumin, total ash, the electronegative and electropositive minerals, nonprotein nitrogen components, vitamins and the essential amino acids. Although previous publications [3] recorded many of the data, the summary values include the results of many determinations heretofore unpublished and the tables show the ranges of all similar data. A paper now in preparation will encompass values for components of human

ponents Observed in Two Successive Lactation Periods, ibid. **43**:1062-1076 (May) 1932. (*v*) Outhouse, J.; Macy, I. G., and Brekke, V.: Human Milk Studies: V. A Quantitative Comparison of Antiricketic Factor in Human Milk and Cow's Milk, J. Biol. Chem. **78**:129-144 (June) 1928. (*w*) Roderuck, C. E.; Coryell, M. N.; Williams, H. H., and Macy, I. G.: Human Milk Studies: XXIV. Free and Total Riboflavin Contents of Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**:171-175 (Sept.) 1945. (*x*) Roderuck, C. E.; Williams, H. H., and Macy, I. G.: Human Milk Studies: XXIII. Free and Total Thiamine Contents of Colostrum and Mature Human Milk, ibid. **70**:162-170 (Sept.) 1945.

4. Coryell and others.[3e] Munks and others.[3s] Roderuck and others.[3x]

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colostrum and milk in comparison with the amounts of the constituents in cow's and goat's milk.[5]

The values for mature milk represent samples collected between fifteen and four hundred and fifty-six days post partum. The frequency distribution of the samples shows a spread throughout the interval, with a greater frequency during the first ten months of lactation:

Weeks post partum....	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64
Number of samples....	96	100	77	67	64	46	29	26	27	18	7	26	0	12	47	11

Proximate Composition.—Colostrum long has been known to have relatively high concentrations of total protein and total ash, which gradually decline as milk flow becomes established (table 1). The concentration of fat and the energy value of colostrum gradually increase during the transition period. The mean concentrations of protein and ash in mature milk are, respectively, 54 and 34 per cent lower than in colostrum, while fat and calories are 54 and 11 per cent higher, respectively. Colostrum and mature milk contain equal concentrations of total solids, but slightly greater amounts were reported in the transitional milk. The lactose content of mature milk is slightly higher than that of transitional milk, whether determined by analyses or by difference.

It is alleged that the superiority of breast milk resides in its relatively high proportion of lactalbumin. Increasing knowledge of the amino acid composition of protein foods and their metabolism in the body indicates that the total amino acid content and distribution in the whole milk are of major importance rather than the amount of an individual protein present in the milk. The total protein contents of colostrum and transitional and mature human milk, as well as the proportions of casein and lactalbumin, are given in table 1.

Electropositive and Electronegative Minerals.—Continually, greater interest is being centered on the amounts and relative proportions of the major electropositive minerals (calcium, magnesium, sodium and potassium) and the electronegative minerals (phosphorus, chlorine and sulfur), since with them the body builds soft and hard tissues and since they are largely responsible for the regulation of the fluids in the body. The acid ash or alkaline ash value of a food in the body may be quite different from its natural acidity, although the terms "acid" and "base" formerly were used frequently to designate the positive and negative minerals in the ionized state. Milk has an acid p_H value but contains an excess of positive equivalents. For growth, the food intake must have an alkaline ash value, i.e., in the body it must provide an excess of electropositive minerals (cations) over electronegative minerals (anions).

5. Macy, I. G.: To be published.

	Source †	Mature Milk (15 Days to 15 Months Post Partum) Samples	Mean	Standard Deviation	Minimum	Maxim
Proximate composition						
Energy, calories	d, r, u	438	74.7	9.3	44.6	110.2
Total protein,‡ Gm.	d, n, r, t, u	583	1.06	0.46	0.73	2.0
Casein,‡ Gm.	n, u	166	0.37	0.08	0.14	0.6
Lactalbumin,‡ Gm.	n, u	163	0.36	0.10	0.14	0.6
Total fat, Gm.	d, n, r, t, u	408	4.54	1.00	1.34	8.3
Lactose (determined), Gm.	d, n, t, u	198	7.1	0.4	4.9	9.1
Lactose (by difference), Gm.	d, n, t, u	313	6.8	0.6	5.0	9.2
Total solids, Gm.	d, n, r, t, u	610	12.9	1.1	10.3	17.1
Total ash, mg.	d, n, r, t, u	390	202.0	18.0	160.0	268.0
Specific gravity §		333	1.031	0.002	1.026	1.03
Minerals ‖						
Electropositive						
Calcium, mg.	d, n, r, t, u	628	34.4	6.7	17.3	60.0
Magnesium, mg.§		302	3.5	0.7	1.8	6.7
Sodium, mg.§		302	17.2	4.5	6.4	43.6
Potassium, mg.§		18	51.2	8.5	37.3	69.5
Total cations, mEq.		...	4.1	...	....	....
Electronegative						
Phosphorus, mg.	d, n, r, t, u	628	14.1	2.5	6.8	26.9
Chloride, mg.	n, r, t	216	37.5	9.0	8.8	73.6
Sulfur, mg.§		116	14	3	5	30
Total anions, mEq.		...	2.8	...	....	....
Ash value (anions plus cations), mEq.		...	6.9	...	....	....
Alkaline ash value (excess cations), mEq.		...	1.3	...	....	....
Amino acid distribution ¶						
Arginine, mg.§		25	43.3	8.8	27.8	63.7
Histidine, mg.§		25	23.7	4.1	12.4	30.2
Isoleucine, mg.§		25	61.0	12.1	40.9	92.3
Leucine, mg.§		25	96.6	17.4	65.3	147.0
Lysine, mg.§		25	70.1	12.7	36.2	92.9
Methionine, mg.§		24	11.6	2.3	6.5	16.9
Phenylalanine, mg.§		25	40.4	6.9	24.3	57.8
Threonine, mg.§		25	51.8	8.5	29.7	65.0
Tryptophane, mg.§		24	19.2	3.0	14.2	26.0
Valine, mg.§		25	72.5	15.5	44.7	114.2
Nonprotein nitrogen						
Total, mg.	j, k, n	151	32.4	5.7	17.3	60.4
Urea nitrogen, mg.	j, k	52	18.0	2.4	12.7	23.5
Uric acid nitrogen, mg.	j, k	56	2.2	0.5	1.3	4.1
Creatinine nitrogen, mg.	k	44	1.1	0.2	0.8	1.9
Creatine nitrogen, mg.	k	41	1.1	0.7	0.2	4.1
Amino acid nitrogen, mg.	j, k, n	157	5.0	1.4	2.8	11.1
Vitamins						
Fat-soluble						
Vitamin A, micrograms.	l	264	61	23	15	226
Carotenoids, micrograms.	l	265	25	11	2	77
Water-soluble						
Total thiamine, micrograms.	x	277	14.2	2.4	8.1	22.7
Free thiamine, micrograms.	x	258	5.3	3.0	1.2	15.9
Total riboflavin, micrograms.	w	272	37.3	8.7	19.8	79.6
Free riboflavin, micrograms.	w	256	24.2	8.2	10.5	61.9
Nicotinic acid, micrograms.	e	268	183	48	66	330
Pantothenic acid, micrograms.	e	269	246	63	86	584
Pyridoxine, micrograms §.		3	18	...	10	22
Biotin, micrograms.	e	266	0.81	0.49	0.04	4.2
Folic acid, micrograms §.		22	0.22	0.07	0.14	0.3
Total inositol, mg.§		7	44.9	...	38.6	53.3
Free inositol, mg.§		5	44.5	...	38.7	52.1
Total choline, mg.§		29	8.9	2.3	5.4	14.3
Free choline, mg.§		3	1.6	...	1.5	1.7
Ascorbic acid, mg.	s	233	5.2	1.9	0.0	11.3

* Values are expressed per hundred cubic centimeters of milk.

† Letters refer to references under corresponding letter in footnote 3 and indicate sources of previously published d methods and discussion.

‡ Quantities of total protein, casein and lactalbumin in the samples were determined by multiplying the value of protein nitrogen in each by the factor 6.37.

§ Unpublished data.

‖ Nine samples of milk, of which 7 were complete twenty-four hour collections from 5 women, contained not more t 50 micrograms of manganese and of copper and only slightly more than 0.5 mg. of iron per hundred cubic centimeters whole milk.

¶ Microbiologic determination.

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Human Milk *

	Transitional Milk (Second 5 Days Post Partum)				Colostrum (First 5 Days Post Partum)				
mples	Mean	Standard Deviation	Minimum	Maximum	Samples	Mean	Standard Deviation	Minimum	Maximum
21	73.5	3.6	67.8	83.0	8	67.1	....	58.8	73.0
44	1.59	0.98	1.27	1.89	33	2.29	1.26	1.46	6.80
2	0.51	...	0.42	0.59	..	....	....	....	....
2	0.78	...	0.69	0.86	..	....	....	....	....
16	3.52	0.73	2.73	5.18	5	2.95	....	2.47	3.15
2	6.4	...	6.1	6.7	..	....	....	....	....
2	6.4	...	6.0	6.8	..	....	....	....	....
46	13.3	0.8	10.5	15.6	29	12.8	1.3	10.0	16.7
16	267	32	231	338	5	308	....	247	350
2	1.035	...	1.034	1.036	..	....	....	....	....
46	46.4	9.5	23.0	62.8	28	48.1	12.1	24.2	65.6
44	3.5	0.6	2.6	5.4	28	4.2	1.3	3.1	8.2
44	29.4	7.6	19.2	53.9	28	50.1	28.0	26.5	136.5
25	63.6	6.8	52.8	76.9	11	74.5	....	65.8	87.0
..	5.5	...	....	....	..	6.8	....	....	....
46	19.8	4.7	9.7	31.7	28	15.7	4.7	8.5	25.1
21	45.7	10.9	30.5	72.1	8	58.6	....	43.5	100.7
19	20	2	15	23	8	23	....	20	26
..	3.7	...	....	....	..	4.0	....	....	....
..	9.2	...	....	....	..	10.8	....	....	....
..	1.8	...	....	....	..	2.8	....	....	....
24	62.8	6.9	47.7	73.4	13	74.4	....	62.0	95.8
24	38.3	4.6	28.8	44.9	13	41.2	....	34.9	46.3
24	97.0	11.0	73.2	120.9	13	101.1	....	88.2	114.9
24	151.2	21.9	113.2	197.0	13	165.6	....	133.4	214.4
24	112.6	15.7	87.7	148.4	12	117.7	....	95.0	141.0
24	24.1	4.0	15.7	34.4	13	25.3	....	18.6	36.2
24	62.4	6.2	48.4	71.3	13	70.0	....	59.9	84.1
24	78.1	7.9	60.6	90.7	13	84.8	....	75.2	103.9
23	28.2	2.4	23.0	31.6	12	32.2	....	25.3	42.2
24	104.9	12.2	77.4	136.0	13	116.9	....	97.8	148.7
2	47.9	...	42.5	53.3	..	....	....	....	....
1	11.1	...	11.1	11.1	..	....	....	....	....
..	....	...	....	....	..	....	....	....	....
..	....	...	....	....	..	....	....	....	....
..	....	...	....	....	..	....	....	....	....
2	4.4	...	4.2	4.7	..	....	....	....	....
26	88	31	58	183	24	161	63	75	305
26	38	10	23	63	24	137	84	41	385
35	5.9	2.2	2.3	10.5	25	1.9	0.6	0.9	3.4
35	0.8	0.3	0.2	1.9	19	0.4	0.2	0.1	0.9
35	36.9	5.3	27.5	49.0	25	30.2	8.7	12.0	45.3
33	24.0	5.3	16.6	40.8	19	19.0	4.4	7.7	27.0
34	175	77	60	360	29	75	22	50	145
33	288	57	135	412	29	183	86	29	302
..	....	...	....	....	..	....	....	....	....
35	0.35	0.40	0.02	1.77	20	0.06	0.06	0.03	0.31
..	....	...	....	....	..	....	....	....	....
..	....	...	....	....	..	....	....	....	....
..	....	...	....	....	..	....	....	....	....
..	....	...	....	....	..	....	....	....	....
..	....	...	....	....	..	....	....	....	....
20	7.1	1.2	4.5	9.0	17	7.2	1.8	4.7	10.4

The mean total ash concentration in mature milk is two-thirds that in colostrum. All the electropositive and electronegative minerals are present in lower concentration in mature milk than in colostrum, but the percentage decreases are not consistent with the 34 per cent reduction in total ash: Calcium shows a 28 per cent decrease; magnesium, 17; sodium, 66; potassium, 31; phosphorus, 10; chlorine, 36, and sulfur, 39. The rate of change to the quantities of components characteristic of mature milk also varies, with the most consistent reductions shown by the percentage decreases in the concentrations of sodium, potassium, chlorine and sulfur in transitional milk, 41, 20, 18 and 30 per cent respectively. In the transitional milk the calcium concentration is only 4 per cent lower than in colostrum but the magnesium concentration is 17 per cent lower, equal to the value for mature milk. Only the concentration of phosphorus is higher in transitional milk than in either colostrum or mature milk. Paralleling the reduction of total ash and the individual minerals as production of mature milk is attained are reductions in the total amounts of positive and negative mineral ions and in the excess of positive over negative ions.

Trace Minerals.—With the use of spectrographic methods, manganese and copper were detected in amounts less than 50 micrograms per nundred cubic centimeters of mature milk and iron in quantities slightly exceeding 0.5 mg. per hundred cubic centimeters. Since in metabolism some of the trace minerals participate in enzyme systems, the field offers opportunities for further valuable research in relation to infant feeding.

Vitamins.—In recent years important roles of the vitamins have been demonstrated in the physiology of cellular activity, hence in the maintenance of life, in growth and in development. Fat-soluble vitamin A and carotenoids are highly concentrated in colostrum, 161 and 137 micrograms per hundred cubic centimeters, respectively, but mature milk contains only 61 and 25 micrograms, respectively. The physical responses of infants to diets containing subminimal amounts of vitamin A depend wholly on the amount of this substance that has been stored in the tissues in utero and during the prior feeding period. If the pabulum has been rich in vitamin A, the body has been able to build a reserve in storage for subsequent need. However, when the current food supply meets only the immediate requirement, storage cannot occur, and a period of low vitamin A consumption unsupported by previous storage may result in nutritional breakdown. Perhaps the high concentration of vitamin A in colostrum has more than passing interest, for in the young infant vitamin A is essential to the integrity of epithelial tissue and to the proper development of teeth, eyes and bony structures.

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The thiamine concentration in colostrum is only approximately 2 micrograms per hundred cubic centimeters, but it is three times that amount in transitional milk (5.9 micrograms per hundred cubic centimeters) and seven times in mature milk (14.2 micrograms per hundred cubic centimeters). For infants this rapid increase in thiamine intake accompanies the readjustment of metabolism and the rapid growth characteristic of the early weeks of life. Thiamine forms an essential part of the enzyme system responsible for carbohydrate metabolism.

Riboflavin, which also is essential to normal metabolism and to adequate skeletal development, is found in colostrum in much greater concentrations than thiamine (30.2 micrograms per hundred cubic centimeters) but in only 24 per cent greater concentration (37.3 micrograms per hundred cubic centimeters) in mature breast milk.

Nicotinic acid increases from 75 micrograms per hundred cubic centimeters in colostrum to 175 micrograms in transitional milk and 183 micrograms in mature milk. Pantothenic acid increases from 183 micrograms in colostrum to 246 micrograms per hundred cubic centimeters of mature milk. Biotin increases from a trace (0.06 microgram) during the first five days post partum to 0.81 micrograms per hundred cubic centimeters of mature milk. Mature human milk contains per hundred cubic centimeters about 0.22 microgram of folic acid, 45 mg. of inositol and 9 mg. of choline. Ascorbic acid is present in concentrations of approximately 7 mg. per hundred cubic centimeters in colostrum and transitional milk but of only 5 mg. in mature milk.

Nonprotein Nitrogen Constituents.—The significance of the nonprotein nitrogen constituents in the physiology of milk secretion, as well as in the nourishment of the baby, has received comparatively little attention. Dietary and other factors influencing milk secretion may be reflected specifically in the nonprotein constituents rather than in the gross composition, and the relative amounts of these constituents may serve as an index of abnormalities in the secretion of milk or of pathologic conditions of the mammary gland itself.[8] On the other hand, the nonprotein nitrogen constituents may filter from the blood directly into the milk. Even though the individual nonprotein nitrogen constituents in milk may be derived directly from the blood, it is possible that they may either maintain equilibrium of composition with that of the blood or vary in concentration, depending on the rapidity and the extent of their utilization in the synthesis of milk proteins and other nitrogenous compounds. The presence of polypeptide nitrogen in fresh human milk as it is expressed from the mammae and its increase as milk is allowed to stand emphasize the necessity of precipitating the fresh milk immediately. The existence of a proteolytic enzyme capable of converting urea to ammonia has been demonstrated.[8]

Amino Acids.—The amounts of the indispensable amino acids in human milk at various stages in lactation also are recorded in table 1. The mean values for all the individual amino acids determined in colostrum, transitional milk and mature milk show reductions in concentration parallel to the lowered concentrations of total nitrogen as lactation is established.

TABLE 2.—*Amino Acids in Proteins of Mature Human Milk* [3b]

	Casein, Mg./100 Cc.	Whey Protein, Mg./100 Cc.	Total, Mg./100 Cc.
Nitrogen	48.6	77.0	125.6
Histidine	6.0	6.3	12.3
Arginine	11.0	29.0	40.0
Lysine	17.3	32.4	49.7
Tyrosine	20.4	29.2	49.6
Tryptophane	5.7	13.0	18.7
Cystine	2.5	17.3	19.8
Methionine	7.2	10.9	18.1
Cystine S	0.7	4.6	5.3
Methionine S	1.5	2.3	3.8
Cystine S + methionine S	2.2	6.9	9.1

TABLE 3.—*Fatty Acids in the Fat of Human Milk* [6]

	Weight Percentage			Molar Percentage		
		Colostrum †			Colostrum †	
	Mature Milk *	First and Second Days	Third Day	Mature *	First and Second Days	Third Day
Saturated fatty acids						
Butyric	0.4	0.2	0.3	1.1	0.7	0.8
Caproic	0.1	0.1	0.1	0.1	0.3	0.2
Caprylic	0.3	0.8	0.1	0.6	1.5	0.1
Capric	2.2	3.5	0.9	3.3	5.3	1.4
Lauric	5.5	0.9	2.6	7.1	1.2	3.4
Myristic	8.5	2.8	4.9	9.6	3.3	5.7
Palmitic	23.2	24.6	27.8	23.4	25.4	28.9
Stearic	6.9	9.9	7.7	6.3	9.2	7.2
Remaining acids calculated as arachidic	1.1	4.9	2.7	0.9	4.1	2.3
Total	48.2	47.7	47.1	52.4	51.0	50.0
Unsaturated fatty acids						
Decenoic	0.1	0.2	0.1	0.1	0.3	0.1
Dodecenoic	0.1	0.1	0.1	0.1	0.1	0.1
Tetradecenoic	0.6	0.1	0.2	0.7	0.1	0.2
Hexadecenoic	3.0	1.8	2.9	3.0	1.9	3.0
Oleic	36.5	36.0	37.1	33.3	33.8	35.1
Octadecadienoic	7.8	7.5	6.2	7.2	7.1	5.9
Octadecatrienoic	0.4	0.3	0.3	0.4	0.3	0.2
Remaining acids calculated as eicosadienoic	2.4	4.6	4.7	2.0	3.9	4.0
Eicosatetraenoic	0.9	1.8	1.6	0.8	1.5	1.4
Total	51.8	52.4	53.2	47.6	49.0	50.0

* Pooled samples of mature milk were taken from 2 women during the twenty-second and forty-third days of lactation.

† Samples of colostrum were procured from 75 women. Collections on the first and second postpartum days were pooled for analysis. Samples were collected under the supervision of Dr. J. P. Pratt, obstetrician, Henry Ford Hospital, Detroit, by two graduate nurses trained in manual expression of human milk.

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The differences in amino acid composition of the casein and whey protein fractions of mature human milk presented in table 2 are of interest. Whey is richer than casein in all seven of the amino acids for which values were determined.

Fatty Acids.—The data in table 3 show the fatty acid composition of human milk fat and are the product of a collaborative effort in which samples of human milk were obtained under controlled conditions by the nursing and laboratory staffs of the Children's Fund of Michigan, carefully preserved and then sent to Dr. Herbert E. Longenecker, University of Pittsburgh, who supervised the analyses.[6] Since the selection of subjects and the methods of collection, handling and preservation were those used in obtaining the samples for the analyses summarized in tables 1 and 2, the values in table 3 are directly comparable.

While specific nutritive values of the individual fatty acids in milk are not defined with any degree of certainty, their distribution in human colostrum and mature milk is of great interest. The results of analyses show that the concentrations of some of the individual fatty acids change coincident with the establishment of mature milk flow.

COMMENT

The milk secreted by different women varies in composition between wide limits. Both the quality and the quantity of the milk secreted may be altered by the amounts and kinds of food consumed; environmental conditions (fresh air, sunshine, work, rest); disease; size and anatomic structure of the mammary glands; hereditary factors, and the emotional makeup of the subject. For any woman there is a definite physiologic capacity of the mammary gland, shown by both the total quantity of milk produced and the length of time lactation persists under normal conditions. Within limits, the normal breast secretes a quantity of milk adjusted to the demand.[3m] Increased output can be procured by placing another infant on the breast or by mechanically or manually[2] expressing the milk at frequent intervals; stimulation of increased flow by completing emptying of the breasts after the baby has nursed can be demonstrated any time after delivery. The work of King,[7] in New Zealand, demonstrated the efficiency of a system including massage, manual expression and hot and cold drenchings in the promotion, maintenance and reestablishment of lactation. Lactation may be maintained

6. Baldwin, A. R., and Longenecker, H. E.: Component Fatty Acids of Early and Mature Human Milk Fat, J. Biol. Chem. **154**:255-265 (June) 1944.

7. King, F. T.: Feeding and Care of Baby, Wellington, New Zealand, Whitcombe & Tombs, Ltd., 1913.

at a high level for over a year in the absence of the suckling reflex,[8] and women with a persistent desire to raise their babies on breast milk despite inverted nipples have expressed their milk manually and successfully fed the milk by bottle.

More accurate knowledge of the composition of the milk a mother secretes for her baby is the key to better understanding of the nutritive requirements of newborn and growing infants and to the development of more adequate substitutes for milk for infants to whom human milk cannot be made available. Methods available for determination of many relatively recently discovered components of milk, notably some vitamins, are of varying accuracy. Chemical entities yet to be discovered may be present and some known to be present have not yet been isolated. Recently, values were reported for folic acid in milk[8a] which demonstrated that microbiologic data obtained with one organism may be many times greater than those obtained with another. Colostrum, the early secretion from the mammary glands, is alleged to contain substances especially needed by the newborn of the species during its physiologic adjustment period following transition from an aquatic existence to an established terrestrial life. New evidence is accumulating which indicates that not only is the well nourished mother less apt to deliver prematurely, but also the nutritional status of her infant is more likely to be good and her chances are better to breast feed her baby satisfactorily.

As Aldrich[9] states:

> It is becoming more and more evident that important things happen to a baby before he is born. The mental and emotional environment of his home may be set at this time; the food his mother eats has an important bearing on his health; his mother's health or illness may decide his welfare or even determine his life or death; the attitude his mother takes in the prenatal period toward breast feeding may influence not only his nutrition but also his feeling of security in the outside world.

Breast feeding has been declining rapidly in the United States,[10] a situation contrasting to that in other countries. Evidence[8] has shown

8. Stewart, H. L., Jr., and Pratt, J. P.: Inhibition of Lactation, Am. J. Obst. & Gynec. **41**:555-563 (April) 1941; Influence of Sucking Stimulus on Lactation, West. J. Surg. **49**:98-103 (Feb.) 1941.

8a. Hodson, A. Z.: The Microbiological Assay of "Folic Acid" as Applied to Milk, J. Nutrition **38**:-25-40 (May) 1949.

9. Aldrich, C. A.: A Health Plan for All Children in a Community, J. Home Econ. **40**:359-360 (Sept.) 1948.

10. Byington, G. M.: Incidence of Breast Feeding in Detroit, Psychosom. Med. **7**:173 (May) 1945. Grulee, C. C.: Breast Feeding, Proc. Interst. Postgrad. M. A. North America (1943), 1944, p. 135. MacNeill, N. M.: Can We Retrieve Breast Feeding? Pennsylvania M. J. **51**:137-140 (Nov.) 1947. Sedgwick, J. P.: Preliminary Report of Study of Breast Feeding in Minneapolis, Am. J. Dis. Child. **21**:455-464 (May) 1921.

that the decline is not due to an increase in the number of mothers who are unable to nurse their babies, a fact which makes it apparent that the major factors are lack of interest or willingness on the part of mothers and failure of fathers and physicians to encourage and aid persistent efforts directed toward establishment of lactation.

Various reports [11] have expressed concern over the decline in breast feeding. Bain [11a] states that

> The incidence of breast feeding is of more than academic interest. . . . Aside from being of value in the solution of emergency problems, knowledge of the incidence of breast feeding in this country is a basic fact about our culture which has validity anthropologically. Any program to change a child-rearing practice needs to rest on a foundation of knowledge of the common existing pattern, as well as on scientific evidence in favor of a different method.

The first nationwide survey of the incidence of breast feeding in the United States, a part of the American Academy of Pediatrics Study of Child Health Services, was limited to the newborn period. It comprised data collected from 2,513 hospitals, which represented more than two thirds of all hospitals in rural and urban areas of all sections of the country having twenty-five or more beds and in which, during the years of the study, there were 1,485,000 births. Bain's [11a] report of the results of the survey concludes that

> For the United States as a whole, one-third of the infants were weaned at the time of discharge from the hospital and two-thirds were on breast or mixed feedings.
>
> A smaller percentage of breast feeding occurred in hospitals in or near metropolitan areas, as contrasted with areas removed from metropolitan centers. A lower percentage of breast feeding occurred in medium-sized hospitals as contrasted with small or large hospitals.
>
> There are striking regional differences, in the northeast the per cent of infants on bottle feeding only—at time of discharge—being 61%, as contrasted with an incidence of 18%, in the southwest and southeast.
>
> Among infants discharged from hospital under eight days of age the incidence of breast feeding was higher than among those who remained longer.

Objectors to the fundamental thesis that breast feeding provides the ideal basic food under optimal physical and psychologic conditions for infants of all ages in the absence of definite contraindications can find little valid support for their criticisms. The factors most frequently emphasized are: the time required for prenatal and postnatal preparation and care of women who nurse their babies; the inconvenience of weighing the infant before and after feeding to determine the amount of food eaten; the greater variability in the composition of human milk

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11. (*a*) Bain, K.: The Incidence of Breast Feeding in Hospitals in the United States, Pediatrics **2**:313-320 (Sept.) 1948. (*b*) Waller, H. K.: Early Failure of Breast Feeding: A Clinical Study of Its Causes and Their Prevention, Arch. Dis. Childhood **21**:1-12 (Jan.) 1946.

from different women than is found in commercial products; difficulties in supplementing the intakes of infants whose mothers do not provide milk in sufficient quantities, and the possibility of the mother's milk being unsuitable for her infant. These conditions do not contraindicate the use of a food which is less expensive, less likely to be a source of infection and widely acknowledged to possess qualities not provided by other formulas.

The problem with premature infants of providing in a restricted volume of fluid sufficient protein and calcium for growth equivalent to that which normally would have occurred in utero has received much attention, although the fact has not been established that for premature infants such growth is necessary or desirable. Potter [12] stated that prematurity is responsible for about one fourth of neonatal deaths and is a contributing factor in another one fourth. She stressed the incomplete development of the premature infants' lungs, kidneys and gastrointestinal tract, and that "human milk is the food of choice for all premature infants," calling attention to the tremendous decrease in infant mortality produced by the program of the Chicago Health Department, in which breast milk was fed routinely to premature infants.

The "wetnurse" has almost disappeared from the American scene. In pediatric practice human milk has proved itself as a medicine as well as a food, and in some urban areas the demand has been met by establishment of "Mother's Milk Bureaus" which function similarly to blood banks. The fact is generally recognized that the emotional influence of breast feeding is important, but one important difference between breast feeding and feeding human milk is frequently overlooked in discussions of the relative value of breast milk and formulas under various conditions: the fact that the breast-fed infant receives colostrum, then transitional milk followed by mature milk, whereas human milk otherwise available to infants is usually mature milk. Further study of the composition of the placental blood which nourishes the fetus and the colostrum which is provided to nourish the newborn infant may be expected to clarify the requirements of premature infants. Progress in artificial feeding of infants can be made by the development of formulas with which the pediatrician can simulate the pattern of nutriments received by nursing infants.

SUMMARY

The results from analyses of several hundred samples of human milk are compiled, and for each of 73 components determined in colostrum, transitional milk and mature milk, data are provided show-

12. Potter, E. L.: The Lessons to Be Learned from a Study of Infant Deaths, J. A. M. A. **124**:336-339 (Feb. 5) 1944.

ing the number of samples analyzed, the minimum, maximum and mean values and the standard deviation.

The samples represented all the milk which could be obtained from both breasts at a regular nursing time by the skilful use of manual expression, the majority representing the pooled collection for all nursing periods in twenty-four hours. Approximately 200 representative healthy, intelligent, cooperative women from varied socioeconomic circumstances provided the samples of milk at the different stages of lactation.

More accurate and complete knowledge of the composition of the milk a mother secretes for her baby is the key to better understanding of the nutritive requirements of newborn and growing infants and to the development of more complete substitutes for milk for infants to whom human milk cannot be made available. This compilation of data on the composition of human milk has special value, since samples representing all the milk secreted by the mammae over a definite period of time were collected and handled similarly, each sample being analyzed by comparably accurate methods for a large number of components, and since they were obtained from healthy women of various socioeconomic levels.

660 Frederick Street (2).

News and Comment

GENERAL NEWS

Continuation Course in Pediatric Roentgenology.—The University of Minnesota, Minneapolis, announces a continuation course in pediatric roentgenology on Oct. 31 through Nov. 5, 1949. The course, which will be presented at the Center for Continuation Study, is intended for roentgenologists and pediatricians. The material to be presented will include the basic medical sciences, clinical medicine and diagnostic roentgenology as it pertains to general and special problems in the field of childhood diseases. Presentation will be by means of lectures, clinics, conferences and round table discussions.

Distinguished visiting physicians who will participate as members of the faculty for the course include Dr. John Caffey, Babies Hospital, Columbia University Medical Center, New York; Dr. Edward B. D. Neuhauser, Children's Hospital, Boston; Dr. Edith Potter, University of Chicago, Chicago, and Dr. Frederic N. Silverman, Children's Hospital, Cincinnati. The remainder of the faculty for the course will be made up of clinical and full time members of the staffs of the University of Minnesota Medical School and the Mayo Foundation.

Grant Approved for Trainee in Psychiatry.—The United States Public Health Service, under the National Mental Health Act, has approved a grant for a trainee in psychiatry at the Walter E. Fernald State School, situated eight miles from Boston. The stipend is level 5, or $3,000 per year. However, candidates at lower levels may be considered and the amount of the stipend adjusted to the level of the candidate's training. Training will be offered in the fields of mental deficiency, child psychiatry and related psychiatric and neurologic problems through supervised experience in the outpatient, inpatient, research laboratory, psychologic, educational and social service departments, as well as through participation in staff meetings and seminars in basic psychiatry and neurology and in child psychiatry.

Applications including the applicant's qualifications or requests for further information should be forwarded to Dr. Malcolm J. Farrell, Superintendent, Walter E. Fernald State School, Waverley 78, Mass.

PERSONAL NEWS

Appointment of Dr. Lee E. Farr Announced.—The appointment of Dr. Lee E. Farr as head of the Medical Department at Brookhaven National Laboratory, Upton, Long Island, N. Y., has been announced by Mr. Michael Amrine, head of public education.

Election of Dr. Rustin McIntosh Announced.—Dr. Rustin McIntosh has been elected president of the Medical Board of the Presbyterian Hospital, New York.

NOTICE

Fall Meeting of Indiana State Pediatric Society Announced.—The fall meeting of the Indiana State Pediatric Society will be on Oct. 14 and 15, 1949, in South Bend, Ind. Dr. W. W. Zuelzer, of Detroit, will speak on "General Diagnostic Principles and Management of the Common Blood Diseases of Children." A clinical session will be held the morning of October 15.

Obituaries

ROCCO JEMMA, M.D.

1866-1949

Rocco Jemma, well known Italian pediatrician and teacher, died on March 24, 1949, at the age of 83 years. He was one of the founders of La Societa Italiana di Pediatria and was its president at its fiftieth anniversary meeting last October. He was a pupil of Prof. E. Maragliano and became one of the leaders in the development of Italian pediatrics. He founded the department of pediatrics at the University of Genoa and later at the University of Palermo. He was made professor of pediatrics at the University of Naples and head of the Ospedali Infantile and Brefotropi in 1896; he retired in 1936 after forty years of active service. In 1926, two volumes containing articles on pediatrics by his Italian confrères and several foreign pediatricians were published and dedicated to him.

H. L. H.

Abstracts from Current Literature

Newborn

WARDS FOR NEWBORN INFANTS. E. MAYERHOFER, Paediat. danub. **1**:5 (Feb.) 1947.

After a brief outline of their historical development, the different types of wards for newborn infants attached to maternity departments and their equipment are discussed.

The first aim of such an arrangement is the prophylactic nutrition of the newborn. The infants fed breast milk should, after the normal stay of eight to ten days, leave the hospital with an increase in weight. Prophylactic measures must be taken concerning proper food for and care of the nursing mothers as well, in order to insure untroubled production of milk.

A breast milk bank of the type first established by Mayerhofer and Pribram in 1909 presents great advantages to such an organization. Schemes making use of boiled breast milk, like the one recommended from Erfurt, must be rejected.

The first prophylactic efforts of the wards for newborn infants are to be followed by suitable care and superintendence of the infants in their own homes. Such supervision should be carried out by public health nurses attached to the departments for newborn infants and the children's hospitals.

FROM THE AUTHOR'S ABSTRACT.

COMPARISON OF WEIGHT OF NEWBORN INFANTS EIGHTY-FIVE YEARS AGO AND TODAY. A. LÜÜS, Paediat. danub. **1**:268 (May) 1947.

The weight at birth of 745 infants born in Stockholm, Sweden, between 1850 and 1860 was compared with that of corresponding groups of infants born between 1935 and 1945.

The average weight of legitimate infants born between 1935 and 1945 exceeded the weight of those born from 1850 to 1860 by 300 to 500 Gm. Similarly, the illegitimate children born between 1935 and 1939 weighed 200 to 300 Gm. more than those born between 1850 to 1854.

The considerable increase in the weights at birth can be explained by the fact that the average standard of living has become high in Sweden, where even the lowest classes are well acquainted with hygiene and where social care is extended to the entire population.

FROM THE AUTHOR'S ABSTRACT.

Acute Contagious Diseases

EOSINOPHILIA AND SCARLET FEVER. A. VAN MEIRHAEGHE, Acta pædiat. belg. **1**:70, 1946-1947.

The first part of the article is a review of the opinions of various authors concerning the occurrence and cause of the high eosinophilic count in scarlet fever. The consensus is that eosinophilia reaches its maximum on the sixth day and that a second peak is reached four to six weeks after the onset. It occurs only in mild and uncomplicated cases. The cause of the eosinophilia is not known; a direct relationship between "eosinophilogenic" substances and the exanthem was claimed, while other authors were of the belief that the increase of eosino-

phils in the blood expresses a state of allergy or is caused by the presence of antitoxin. The author cites his own observation in 18 cases, and he comes to the same conclusions as the reports from the literature previously indicated. Since cases with complications do not seem to show eosinophilia in the first six days of the disease—as the mild uncomplicated cases do—he suggests the use of this phenomenon for prognostic purposes.

GLASER, Chicago.

ACTION OF AEROSOL PENICILLIN ON CORYNEBACTERIUM DIPHTHERIA. J. LEGROS, Acta pædiat. belg. **1**:80, 1946-1947.

After reference to a previous publication by the same author (Treatment of Diphtheria Carriers with Aerosols of Sulfapyridine, *Presse méd.* **51**:332 [June 19] 1943) in which aerosol inhalation of a 10 per cent solution of sulfapyridine for the treatment of diphtheria carriers was described, the article proceeds to discuss in vitro experiments with penicillin. A solution of 25,000 units of penicillin per cubic centimeter was vaporized in a cage of 700 cu. dm., and cultures of Corynebacterium diphtheriae were exposed to the fumes. The cultures did not grow. The solution, when preserved on ice, was found to be stable for ten days. When kept at higher temperatures, it lost its effectiveness earlier. In his human experiments, the author treated 34 diphtheria carriers with four daily inhalations of 1 cc. of isotonic sodium chloride solution containing 25,000 units of penicillin. Thirty-one carriers proved to be cleared after four days; 3 had to be treated another four days.

GLASER, Chicago.

Acute Infectious Diseases

AN OUTBREAK OF INFLUENZA A IN A BOYS' SCHOOL. THEODORE H. INGALLS, J. ROSWELL GALLAGHER and JOHN F. ENDERS, New England J. Med. **235**:786 (Nov. 28) 1946.

An epidemiologic and clinical description of infections of the upper respiratory tract occurring in a boys' boarding school in January and February 1946 is given. Of 680 students, 215 became ill.

Complement fixation tests were made for influenza A and B on the serums of 8 boys during convalescence and of 7 others during both the acute and the convalescent phases. The average titer against influenza A among the convalescent patients was found to be more than double that considered presumptive evidence of recent infection. When the seven paired serums were tested, the average titer during the convalescent phase was found to be approximately ten times that during the acute phase.

As determined on the basis of the serologic evidence in this outbreak, the virus of influenza A appeared to be the predominant etiologic agent.

FROM THE AUTHORS' SUMMARY.

AMBULATORY TREATMENT OF INFANTILE GONORRHEA BY ORAL ADMINISTRATION OF PENICILLIN. A. WIEDERHOLD and A. MENDEZ, Arch. argent. de pediat. **26**:404 (Dec.) 1946.

Twenty-five out of 26 patients with infantile gonorrhea were successfully treated by oral administration of penicillin. The children, most of whom were followed for a period of more than six months, presented a cure as much bacteriologic as clinical. The patients went through a reactivation with strong protein silver (protargol®) and neogynergen® (a preparation containing ergotamine tartrate and ergonivone tartrate).

The authors conclude from the results obtained that penicillin administered orally is absorbed and eliminated by the urine in sufficient quantity and rapidly enough to destroy gonococci without a constant concentration of the drug in the blood being necessary. They consider that obtaining good results in the treatment of infantile gonorrhea by the oral administration of penicillin is a matter of using proper doses. The simplicity and the other advantages of this type of treatment deserve the consideration of the practitioner.

ROJAS, Boston.

Chronic Infectious Diseases

BCG VACCINATION IN SWEDEN. ARVID WALLGREN, Paediat. danub. **1**:213 (April) 1947.

Vaccination with BCG was started in Sweden in 1925. At first vaccine obtained from the Institute Pasteur was used, but since 1927 a preparation derived from the original strain has been made in Göteborg, Sweden. Its virulence is checked on animals and its purity by culture. The first vaccinations were made orally, but for the last twenty years preference has been given to the intradermal and percutaneous methods.

The vaccination aims at giving immunity by rendering the organism sensitive to tuberculosis without causing the disease. If the sensitization is successful, the tuberculin reaction becomes positive. The vaccination does not eradicate tuberculosis but prevents the grave consequences of the primary stage. Vaccinated persons may also acquire the disease if exposed to massive infection, but the illness will present itself in the secondary stage only and its course will be a light one.

At first, inoculations were given only to children who were not carriers of virulent bacilli, who gave negative reactions to 1 mg. of tuberculin and who could be isolated for six to eight weeks. After it had been proved that the vaccination carried no danger, its application became widespread. In Sweden vaccination is obligatory for students in nursing schools. A campaign has been started in which inoculation not only of all newborn infants but also of school children, apprentices, university students and soldiers is advocated. Should the reaction to tuberculin still be negative six weeks after the vaccination, the procedure is repeated until the reaction to the test becomes positive. Repetition of the vaccination is indicated at the age of 3 years and with students and apprentices at the completion of the school years.

FROM THE AUTHOR'S ABSTRACT.

PRIMARY CUTANEOUS TUBERCULOSIS. J. TAMÁSI, Paediat. danub. **1**:225 (April) 1947.

To make a valid diagnosis of cutaneous tuberculosis of primary nature, the following points should be observed: 1. A primary complex, proved by the means of histologic and bacteriologic study, must be present. 2. Tuberculous allergy must develop simultaneously with the primary complex. 3. The source of the infection should, if possible, be traced.

A case of a child 18 months of age is described, in whom a primary cutaneous complex, fulfilling the previously mentioned requirements, was discovered. The initial lesion was lupus like; the regional lymph nodes underwent caseation and perforation. Operative removal of the cutaneous focus and the lymph nodes resulted, after a short recurrence, in complete recovery.

FROM THE AUTHOR'S ABSTRACT.

VACCINATION WITH BCG. C. PREISICH, Paediat. danub. **1**:245 (April) 1947.

The human organism, with its natural vitality, fights with success against tuberculous infection. If the vitality is unimpaired, antibodies are formed to combat the effect of the antigen originating from tuberculin. This is the specific factor in immunity. To know its extent, not only has the state of allergy to be checked at various times but the vitality itself should also be observed. If the vitality is good, the disappearance of allergy means the cessation of specific immunity.

With children who are often exposed to tuberculous infection, BCG vaccination should be repeated at the age of 3 years. FROM THE AUTHOR'S ABSTRACT.

SYPHILITIC DACTYLITIS. J. FRANKL and D. SOMOGYI, Paediat. danub. **1**:252 (April) 1947.

Phalangitis is a rare symptom of congenital syphilis. It begins mostly on the first phalanges. The digit develops a bottle-shaped swelling, but the soft tissues and articulations are not affected. The early form is not liable to suppurate and responds well to treatment. However, it may not present itself until the second year, when an abscess generally forms.

In the case reported, dactylitis occurred on the second and fourth fingers of a 10 week old infant of a syphilitic mother. Five days later pseudoparalysis of the forearm due to syphilitic osteochondritis developed. The condition subsided after a month's treatment.

Differentiation from tuberculous dactylitis may present difficulties. In the roentgenograms of this infant, the process on the fourth digit was characteristic of tuberculosis but that on the second finger was similar to a syphilitic lesion.

FROM THE AUTHORS' ABSTRACT.

Diseases of Blood, Heart and Blood Vessels and Spleen

RETICULOENDOTHELIAL FUNCTION BEFORE AND AFTER BIRTH. I. CSEFKÓ, Paediat. danub. **2**:10 (July) 1947.

It is the passive immunity inherited from the mother that protects the newborn infant against infections. Active immunization is unsuccessful, or successful only to a small extent, until some weeks have elapsed. In order to clarify the cause of this, the function and the susceptibility of the reticuloendothelial system were examined in rat embryos.

Embryos, 14 to 16 days old, were removed from the uterus without interrupting the connection between them and the mother rat. India ink was then injected into the umbilical vein. No storage could be discovered in the Kupffer cells of the liver, only some absorption of the finest granules. In the other cells of the reticuloendothelial system only thrombi could be seen.

A slight storage was observed in the hepatic cells when 1 mg. of histamine was given intravenously before the india ink.

If the india ink was, however, given subcutaneously, the granules were stored well by the hepatic cells, but not by the other cells. The skin, the capillaries of which are usually able to store india ink following an injection of histamine (Jancsó's phenomenon), does not react at this age either.

The conclusion is drawn that the protective function of the reticuloendothelial system does not operate until some weeks after birth and that the spontaneous

capacity for storing and the irritability are characteristics developing during ontogenesis.

This is the reason that resistance to certain infections is so low during a time following birth and that the possibility of active immunization is slight at this time. The irritability of the reticuloendothelial system is restricted to the liver and its activity and capability to react develop only gradually, probably because of some hormonal effect.

FROM THE AUTHOR'S ABSTRACT.

Diseases of Nose, Throat and Ear

FOREIGN BODIES IN THE RESPIRATORY TRACT. JOHN R. RICHARDSON, New England J. Med. **235**:707 (Nov. 14) 1946.

The diagnosis of a foreign body in the respiratory tract is easy when one remembers to think of the possibility. The story of the patient or that of the patient's family should be believed until proved wrong. Roentgenologic examination should include the entire respiratory and digestive tracts. Fluoroscopy of the chest is indicated when a nonradiopaque foreign body is suspected. Unless a foreign body can be completely visualized, it is dangerous for one to attempt its extraction. The safe removal of a foreign body is aided by reference to a duplicate, as well as roentgenologic study, so that its exact position and location are understood. Only then can removal be accomplished without the possibility of doing more harm than good through unwise manipulation.

FROM THE AUTHOR'S SUMMARY.

MASSIVE ATELECTASIS FOLLOWING TONSILLECTOMY UNDER LOCAL ANESTHESIA: REPORT OF A CASE. LEROY L. SAWYER, Arch. Otolaryng. **46**:45 July) 1947.

A 25 year old white woman showed massive collapse of the right lung following tonsillectomy under local anesthesia. Through the bronchoscope a bloody mucous plug was aspirated from the right main bronchus, following which there was immediate improvement. Bronchoscopy is the treatment of choice.

KIMBALL, Evanston, Ill.

LOCAL USE OF PENICILLIN IN ALCOHOL AND GLYCERIN FOR CHRONICALLY RUNNING EARS. AUBREY G. RAWLINS, Arch. Otolaryng. **46**:71 (July) 1947.

Instillations twice daily of equal parts of 70 per cent alcohol and saturated glycerin solution, with 1,000 units of penicillin added for each cubic centimeter, is good local treatment for chronically draining ears. The rationale and exact regimen are described.

KIMBALL, Evanston, Ill.

INFANT SPEECH: VARIABILITY AND THE PROBLEM OF DIAGNOSIS. ORVIS C. IRWIN, J. Speech Disorders **12**:287 (Sept.) 1947.

This is a report on the diagnostic use of percentile curves for both phoneme type and phoneme frequency in the speech of infants. Equations have been derived from the data and curves plotted for the tenth, twenty-fifth, fiftieth, seventy-fifth and ninetieth percentiles. The diagnostic use of the curves is explained and illustrated.

PALMER, Wichita, Kan.

SPONTANEOUS VERSUS IMITATED VERBALIZATION IN TESTING ARTICULATION IN PRESCHOOL CHILDREN. MILDRED C. TEMPLIN, J. Speech Disorders **12**:293 (Sept.) 1947.

Most speech clinics test articulatory defects by showing children pictures of objects designed to elicit specific sounds. Little experimental research is available on whether this is better than saying the word directly for the child and having him repeat it. One hundred children, 56 boys and 44 girls, ranging in age from 2 years 1 month to 5 years 9 months, were included in this study. A total of 214 tests were made. The observer's reliability on these tests was measured. Three measures of the child's articulation were obtained in each test session. The first measure, designed as a picture test, was the articulation of specific sounds in words uttered spontaneously in response to pictures. The second measure, aural test A, was his response when he had the word pattern of the examiner to imitate and the picture was still before him. The third measure, aural test B, made at the end of the test session, was his repetition of each of the words after the examiner with the picture no longer before him. Results for each were as follows: 1. The presence or absence of pictures in the imitative situation did not influence the result. Gains in articulation with age when measured by each of the three methods are similar, and the correlation coefficients with chronologic age are similar. 2. In measurement of the production of specific sounds, similar results are obtained by spontaneous and imitative methods. 3. Similar results for specific sounds are obtained when the same sound is presented in different words.

PALMER, Wichita, Kan.

THE EFFICACY OF SPEECH RE-EDUCATION OF FUNCTIONAL ARTICULATORY DEFECTIVES IN THE ELEMENTARY SCHOOL. GLADYS REID, J. Speech Disorders **12**:301 (Sept.) 1947.

So-called functional articulatory defects, as defined in this paper, decrease rapidly with age. A review of the literature on this problem is given. An experimental group of 38 children in grades 1 through 7 was selected for whom there was no program of speech correction. These children had at least normal intelligence, no organic anomalies and no apparent etiologic difficulties concerning the functional articulatory defect. All children were given speech articulation tests at the beginning of the experiment and at the end, with an interval of about six months. A control group of 41 children was selected from grades 1 through 8 on the same basis from other schools than those in the experimental group. The corrective work carried on was of the group therapy type. There was only slight improvement in the control group, while in the children receiving corrective care there was considerable improvement and some correction. It is possible to infer that (1) the described system of correcting articulatory defects in the elementary school is effective; (2) although maturation plays a part in a child's learning to speak correctly after he enters school, it is at best a slow process compared with the speech improvement effected by special speech training.

PALMER, Wichita, Kan.

THE PLACE OF NEW YORK CITY IN AMERICAN LINGUISTIC GEOGRAPHY. C. K. THOMAS, Quart. J. Speech **33**:314 (Oct.) 1947.

The speech of New York city is a distinct dialectic variant of Eastern speech. Speech teachers by precept and example should teach good New York city speech to New York city students.

PALMER, Wichita, Kan.

PUNCTURE AND SURGICAL OPENING OF THE ANTRUM IN INFANTS. J. HERMANNE, Acta pædiat. belg. **1**:76, 1946-1947.

Otomastoiditis is classified into acute and chronic types. The chronic type causes diagnostic difficulties and calls for surgical opening of the antrum. To facilitate the diagnosis, the author suggests the puncture of the antrum in every child suspected to have otomastoiditis. Behind the posterior-superior angle of the external canal, in the retroauricular fossa, a trocar is inserted until the sudden lessening of resistance indicates the entrance of the point of the needle into the antrum. At this point material is aspirated and serosanguineous, mucopurulent or frankly purulent fluid is obtained. The healthy antrum is empty. Direct microscopic examination and culture of the material are done. The amount and character of the fluid obtained and the general condition of the patient are considered as indicators for the need of an operation. Hermanne has performed 140 punctures on 65 children. He concludes from his observations and from the literature that the puncture is a worth while diagnostic procedure which aids in the early detection of otomastoid infection in patients who may have gastrointestinal disturbances with no symptoms pointing toward the real cause of their trouble: otomastoiditis.

GLASER, Chicago.

HERPETIC ANGINA IN SUCKLING. D. V. BORI, Policlinico inf. **15**:314 (July) 1947.

The author describes a certain kind of "angina herpetica" that attacks sucklings, the anatomic form of which is more like herpes than aphtha. This form of the illness has little general symptomatology; it shows a particular localization and blood picture, never evolving into aphtha, and a conspicuous decrease in the weight of the suckling precedes the illness.

FROM THE AUTHOR'S SUMMARY.

Diseases of Lungs, Pleura and Mediastinum

A CASE OF PULMONARY HYDATID CYST WITH ASTHMA. M. S. BISHR, J. Roy. Egyptian M. A. **30**:341 (July) 1947.

Bishr reports a case of pulmonary hydatid cyst in a 10 year old boy, who came to the hospital complaining of repeated attacks of cough, dyspnea and wheezing. These attacks were relieved by administration of ephedrine hydrochloride. Examination revealed signs suggestive of asthmatic bronchitis with pleural effusion. Operation revealed the typical Echinococcus scolices.

McGUIGAN, Evanston, Ill.

PNEUMOCOCCAL EMPYEMA TREATED WITH PENICILLIN. H. M. M. MACKAY, Proc. Roy. Soc. Med. **39**:696 (Sept.) 1946.

This case of pneumococcic empyema treated with penicillin was reported in a child 8 months of age.

WILLIAMSON, New Orleans.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

FIBROCYSTIC DISEASE OF THE PANCREAS (TWO CASES). DONALD PATERSON, Proc. Roy. Soc. Med. **39**:586 (Aug.) 1946.

Two cases of fibrocystic disease of the pancreas are reported.

The first was of a girl, aged 8 months. Her progress while in the hospital was highly unsatisfactory. The child died and postmortem examination confirmed

the diagnoses. A section of pancreas showed increased fibrosis and dilatation of the ducts.

The second case was of a girl 4 years of age whose progress was satisfactory on treatment. However, she was still susceptible to respiratory infections. The results of physical examinations, investigations and treatment of both patients accompany the reports.

WILLIAMSON, New Orleans.

FIBROCYSTIC DISEASE OF THE PANCREAS. BERNARD SCHLESINGER, Proc. Roy. Soc. Med. **39**:587 (Aug.) 1946.

This case of fibrocystic disease of the pancreas was reported in an infant 10 months of age. The history and results of physical examination, investigations and treatment are given in the report.

WILLIAMSON, New Orleans.

Nervous Diseases

HEREDITARY SCLEROSES. OTTO MARBURG, Arch. Neurol. & Psychiat. **55**:338 (April) 1946.

The author limits hereditary scleroses to those conditions in which glial proliferation replaces, in succeeding generations, destroyed parenchyma which is of constitutionally degenerative nature. He distinguishes four groups: multiple sclerosis, diffuse sclerosis, combined sclerosis and Pelizaeus-Merzbacher disease (degenerative form only). Only about 100 cases of the familial type of multiple sclerosis have been observed.

Diffuse sclerosis has been divided into (*a*) acute infantile (Krabbe), (*b*) subacute juvenile (Scholz), (*c*) adult (Ferraro) and (*d*) chronic (Pelizaeus-Merzbacher) conditions. The number of these conditions on a heredofamilial basis is relatively small. Even though occurring in families, the majority of them are not hereditary; the author feels that most forms are exogenous, the infantile form not being heredofamilial at all. The juvenile type may be heredofamilial and Pelizaeus-Merzbacher disease is always so.

BEVERLY, Oak Park, Ill.

CONGENITAL FACIAL PARALYSIS. J. P. MURPHY and W. J. GERMAN, Arch. Neurol. & Psychiat. **57**:358 (March) 1947.

Congenital facial paralysis is usually bilateral, has paralysis of the abducens nerve associated with it and is commonly accompanied with other evidence of faulty development of the brain stem and cervicobrachial region.

BEVERLY, Oak Park, Ill.

TOPOGRAPHIC DISTRIBUTION OF LESIONS IN CENTRAL NERVOUS SYSTEM IN JAPANESE B ENCEPHALITIS: NATURE OF THE LESIONS, WITH REPORT OF A CASE ON OKINAWA. WEBB HAYMAKER and ALBERT B. SABIN, Arch. Neurol. & Psychiat. **57**:673-692 (June) 1947.

A detailed study of a case of Japanese B encephalitis occurring in a member of the United States armed forces in Okinawa, in which the duration of the illness was approximately ten days, revealed a striking involvement of the gray matter of the central nervous system, relative sparing of the white matter and absence of change in the peripheral nerves and in the thoracic and abdominal viscera. The structures most severely affected were the thalamus, the substantia nigra, the nucleus basalis and the anterior horns of the spinal cord, where the lesions tended

to be confluent, and the cerebral cortex and the cerebellum, where they generally were discrete. The presence of neuronophagic nodules in all portions of the gray matter was taken as compelling evidence of damage to ganglion cells by the virus. These nodules, generally spoken of as "glial," the authors regard as composed of hematogenous and adventitial mononuclear cells.

FROM THE AUTHORS' CONCLUSIONS.

EPIDEMIC ENCEPHALITIS IN MILITARY PERSONNEL: ISOLATION OF JAPANESE B VIRUS ON OKINAWA IN 1945, SEROLOGIC DIAGNOSIS, CLINICAL MANIFESTATIONS, EPIDEMIOLOGIC ASPECTS AND USES OF MOUSE BRAIN VACCINE. ALBERT B. SABIN, J. A. M. A. **133**:281 (Feb. 1) 1947.

An epidemic of Japanese B virus encephalitis occurred on Okinawa in September 1945, with 38 suspected cases among American military personnel and 12 definite cases (11 proved serologically) with 2 deaths. Neutralizing and complement-fixing antibodies were studied. The latter was found to be the method of choice for practical purposes of diagnosis. Clinical symptoms included drowsiness, mental confusion and coma. High fever and nuchal and spinal rigidity, with leukocytosis and pleocytosis of spinal fluid, were the chief clinical manifestations.

Ninety per cent of 30 Okinawan natives over 20 years of age without history of encephalitis gave serologic evidence of having had the disease. The percentage decreased progressively as the age decreased. Antibodies were demonstrated in Okinawan horses, goats and in 1 cow, but not in chickens. Cases occurred chiefly in proximity to civilian foci and where the mosquito control was inadequate.

Mouse brain vaccine was administered to more than 60,000 persons in 1945 and to 250,000 in 1946. Data concerning the protection afforded are lacking. Three cases of "neuritis" and 3 of infectious polyneuritis were probably not related to vaccination. No cases of demyelinating encephalopathy occurred.

BAIRD, Wauwatosa, Wis.

GENETC RELATIONSHIPS BETWEEN SPINAL HEREDITARY SCLEROSIS (FRIEDREICH'S ATAXIA) AND VARIOUS FORMS OF TAPETORETINAL DEGENERATION. A. FRANCESCHETTI and D. KLEIN, Bull. schweiz. Akad. d. med. Wissensch. **2**:321 (May) 1947.

In the Argovian family "Glaser" with hereditary sclerosis of the spine (Friedreich's disease), 21 cases of hereditary ataxia and 4 cases of progressive macular degeneration have been observed (*Arch. d. Julius Klaus-Stiftg. f. Vererbgsforsch.* **16**:469, 1941). Now the authors report the occurrence of retinitis pigmentosa and retinitis punctata albescens in two further branches of this family. The pigmentosa group consisted of 9 siblings descended from consanguineous marriages. Four of them were affected. In addition, kyphoscoliosis, hypogenitalism and neuropathic stigmas were also observed in this group. In the albescens group, with 2 affected siblings, consanguinity of the parents was not proved but was assumed. In contrast to the homochronous occurrence of the condition, the homology of the morbid symptoms and the progressive course as observed in the pigmentosa group, the two albescens siblings showed differences, with rapid progress of the disease in the sister and a somewhat milder and slower-developing form of the disease in her younger brother.

Because of the near relationship of the sclerotic and tapetoretinal groups, the children's common descent from the same ancestor (Ludwig "Glaser," 1510-1565) and the narrow clinical and genetic relationships between the central nervous system and the visual apparatus, the authors express their opinion that the cases

of hereditary sclerosis and the particular forms of tapetoretinal degeneration are probably phenotypical variations of the same hereditary degenerative predispositions, i. e., so-called equivalents.

FROM THE AUTHORS' SUMMARY.

Psychology and Psychiatry

CHILD GUIDANCE. L. LIEBERMANN, Paediat. danub. **1**:301 (May) 1947.

In 1938, the pediatric department of the University of Budapest, Hungary, organized a special outpatient clinic for the guidance and treatment of maladjusted children. The center carries out psychologic diagnostic work and, in a limited number of cases, psychotherapy. The age of patients varies from 1 to 18 years.

Its aims are twofold: psychologic research work and treatment of urgent cases. Psychologic diagnosis is based on the analysis of intelligence, emotional life and behavior. The technic applied is the customary child guidance technic. It is founded on observation and analysis of surroundings, their effects and the reactions of the individual child to these. The relationship of child and mother, as the first emotional conditioning process, is considered extremely important.

The author concludes that most infantile psychologic conflicts are actual conflicts. Most children are favorably influenced by the usual guidance technic, and pavor, enuresis and fear conditions especially have a favorable prognosis. There have been many cases of social misconduct since the war, especially stealing.

The results indicate an increase of infantile neuroses, as a direct consequence of the war, which are caused by the disturbances of adults and children caused by emotional traumas and unstable conditions.

FROM THE AUTHOR'S ABSTRACT.

Diseases of the Genitourinary Tract

RENAL DWARFISM IN A NURSLING. M. LAPLANE, M. OEHMICHEN and M. LHERMITTE, Arch. franç. de pédiat. **3**:316, 1946.

The authors followed this patient for fifteen months after the first examination at the age of 19 months. A striking feature of the infant's illness was serious hypotrophy. The weight, which was 8½ pounds (3,856 Gm.) at birth, reached 15½ pounds (7,031 Gm.) at 19 months. The baby's stature was likewise arrested. Advanced rickets and renal insufficiency with chronic nephritis were also present. These disorders formed the classic triad of renal rickets with dwarfism. A familial factor was discovered during the investigation.

AMESSE, Denver.

OPERATIVE INTERVENTION IN A HERMAPHRODITE. H. ROUÈCHE and E. LACKMANN-AVENEL, Arch. franç. de pédiat. **3**:322, 1946.

One of the authors presented this patient in a previous session of the Pediatric Society of Paris. The type of hermaphrodism conformed to the description given of gynandroid cases, in which a female hermaphrodite has the appearance of a male. Sudden and acute pain in the left inguinal region was diagnosed as ectopic testis and an abdominal section was made. The findings included an infantile uterus, two ovaries and, attached to the uterus, a testis. Since the subject had expressed a desire to preserve masculine elements, bilateral ovarian castration was performed and the testicular artery allowed to function. The ectopic testis was then removed through incision in the left inguinal canal. The surgical urgency, therefore, served to demonstrate what may be called a case of true hermaphrodism.

AMESSE, Denver.

GENITAL MALFORMATION IN A NEWBORN INAFNT: REPORT OF A CASE. E. G. CASELLI and R. J. DELLEDONNE, Arch. argent. de pediat. **26**:261 (Oct.) 1946.

The genital malformation reported consisted of a central penis-like organ, 1 cm. long. The glans penis bent downward and was covered by an imperforated foreskin in which a suggestion of an orifice was present. No urethra was identified; in its stead a cordlike structure in the ventral aspect of the penis was observed. From the root of the central organ two longitudinal folds resembling labia majora were present; these folds had transverse wrinkles. A central cavity resembling the vagina, 3 cm. deep, was seen. In the bottom of this cavity was a small orifice communicating with the bladder. No uterus or testes were identified. A laparotomy was advised, but it was refused by the parents. ROJAS, Boston.

Diseases of the Ductless Glands: Endocrinology

THE EFFECT OF THIOURACIL ON THE SUCCINOXIDASE AND CYTOCHROME OXIDASE OF RAT LIVER. SAMUEL R. TIPTON and W. L. NIXON, Endocrinology **39**:300 (Nov.) 1946.

There is considerable evidence that thiouracil depresses the ability of the thyroid gland to form or release hormone. In the course of their studies on the thyroid and adrenal glands and the relation of their hormones to oxidation enzyme systems, the authors noted that, after oral administration of thiouracil, the activities of the succinoxidase and the cytochrome oxidase of hepatic homogenates from rats were less than those from control rats. They were interested in determining whether this depression was a direct action of the drug on the enzyme systems of the liver or an indirect action through the level of circulating thyroid hormone. The data presented in this paper offer further support of the concept that the action of thiouracil is on the thyroid gland and any action on peripheral tissues is a consequence of this primary action on the thyroid. JACOBSEN, Buffalo.

EFFECTS OF VARIOUS HORMONAL CONDITIONS IN THE INTACT RAT ON THE SYNTHESIS OF SERUM CHOLINESTERASE. CHARLES H. SAWYER and JOHN W. EVERETT, Endocrinology **39**:307 (Nov.) 1946.

Nonspecific cholinesterase is many times more concentrated in the serum of mature female rats than in the serum of male rats.

Long-term trends in the serum enzyme levels were determined, and they were observed to parallel the estrogen level but to be independent of the progesterone level. Estrogen does not affect the activity of cholinesterase directly, rather, the hormone stimulates synthesis of the enzyme. JACOBSEN, Buffalo.

ADDISON'S DISEASE AND A NONSPECIFIC ADDISON SYNDROME IN CHILDREN. VILÉM J. MATHESIUS, Pediat. listy **2**:160, 1947.

The author describes a case of beginning Addison's disease in a boy aged 10; on admission in July 1946 the patient was without pigmentation. The diagnosis was based on the clinical picture of striking lethargy and on laboratory findings. Treatment was with desoxycorticosterone acetate injected in oil solution and a diet rich in salts. After the patient's recovery from the acute stage, 1 tablet containing 100 mg. of corticosterone was implanted subcutaneously. A transient crisis was precipitated several months later by influenza. The patient was readmitted to the hospital and treated again with injections of corticosterone and

a diet rich in salts. Recovery was rapid and complete, so that his behavior was that of a normal boy of his age. At the second admission slight yellowish brown pigmentation was already obvious. On control admission in March 1947 the boy's general condition was excellent, slight pigmentation of the linea fusca being present. The cause of the disease has not yet been found; all examinations to detect a tuberculous process had negative results.

The second part is a preliminary report of serious conditions in infants and small children due to pneumonia, influenza of various types, otitis media and enteritis, which are explained by the author as a temporary insufficiency of the adrenal cortex, or a transient addisonism. The good result of treatment with derivatives of corticosterone administered in oil solution, combined with a diet rich in salts, which treatment the author advocates also for infants, is described.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Muscles, Bones, Joints and Lymph Glands

OSTEOMYELITIS IN INFANCY. ORESTE MAZZARELLA, Arch. ital. pediat. e puericolt. **11**:317, 1946.

From Jan. 1, 1938 to June 1945, 64 children with infantile acute hematogenous osteomyelitis were admitted to the surgical section of the pediatric clinic in Rome. The incidence of this condition in relation to that of other surgical diseases in the same hospital in comparison with previous years redoubled in 1944 and quadrupled in the first six months of 1945. Similarly, the mortality rate in the period 1944 to 1945 was quintupled. The increase in mortality and morbidity was in infancy. The curve for frequency was compared with those for hygienic and alimentary disorders of World War I and the postwar period. In infancy the micro-organism usually recovered is Staphylococcus aureus, although the hemolytic streptococcus was the only organism isolated in this period.

The lack of agreement with Green and Shannon's data (Osteomyelitis of Infants: A Disease Different from Osteomyelitis of Older Children, *Arch. Surg.* **32**:462 [March] 1936) was due to the increased occurrence of pyodermatitis in relation to the infections of the respiratory tract which preceded the disease in these infants.

The statistics presented in this report are especially of interest concerning the location of the infectious process, the apparent immunity of the radius, the greater frequency in infancy of osteomyelitis in the humerus than in the tibia (the opposite occurs at a later age) and lack of predilection for the more fertile metaphysis.

FROM THE AUTHOR'S SUMMARY.

OSTEOMYELITIS SIMULATING SYPHILITIC OSTEOCHONDRITIS. L. STRAUSZ, Orvosok lapja **3**:331 (March 15) 1947.

A 3 month old infant showed the following clinical symptoms: coryza, paronychia and painful immobilization of the left arm (like Parrot's pseudoparalysis). The serologic reactions were doubtful. The roentgen picture showed the typical sign of osteomyelitis and syphilitic osteochondritis with considerable periosteal thickening. The infant died after a few days, and the postmortem examination revealed streptococcic sepsis with osteomyelitis (epiphysitis) of the left arm. No traces of syphilitic infection were discovered.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

SUBLUXATION OF THE FOOT, OR CLUBFOOT. P. MARIQUE, Presse méd. **54**:411 (June 22) 1946.

Clubfoot is primarily a subluxation of the foot on the lower part of the leg, as is shown by lateral roentgenograms of the ankle. Unless this condition is corrected, other treatment will be of no avail. The author advises that manipulation be deferred until the infant is a month old because of the fragility of the ankle in the newborn. The maneuvers should be made without too much force, preferably with anesthesia.

DAFFINEE, Melrose, Mass.

PERIOSTEAL DYSPLASIA: A CASE OF SPONTANEOUS CURE. JACQUES LEVEUF, Arch. franç. de pédiat. **3**:315, 1946.

The history of the patient, 18½ years of age, revealed that the first fracture was sustained at the age of 2 months. From that time on there were recorded fractures of one or more bones annually until the appearance of the menses. The bones affected were those of the lower limbs and the right humerus; in addition to the fractures, there were dislocations of the shoulder and elbow. On examination, the subject was classified as a dwarf, 43.6 inches (111 cm.) tall, weighing 77 pounds (31.8 Kg.) and presenting numerous deformities of the thighs, legs and right arm, with lumbar scoliosis and parietal bosses. Roentgenograms demonstrated generalized decalcification.

AMESSE, Denver.

Diseases of the Eye

THE SURGICAL TREATMENT OF STRABISMUS. D. B. KIRBY, Am. J. Ophth. **29**:408 (April) 1946.

Kirby is of the opinion that operation may well be performed at an early age when strabismus is not corrected by orthoptic measures and that operation may be planned beforehand, but the actual details and extent of the procedure may not be evident until the muscles are exposed. It is better to do too little than too much and, if further surgical intervention is necessary, to wait until the tissues have healed and resolved. He urges proper care and orthoptic training after operation.

W. S. REESE. [ARCH. OPHTH.]

SPONTANEOUS RUPTURE OF THE LENS CAPSULE IN ANTERIOR LENTICONUS. L. H. EHRLICH, Am. J. Ophth. **29**:1274 (Oct.) 1946.

Ehrlich reports the case of a 12 year old boy who first noted defective vision in the right eye three years before, following a mild blow in a fist fight. Vision in this eye was 4/200, and examination with the slit lamp revealed a bulging forward of the anterior capsule in the axial region. This elevation seemed filled with a clear fluid. A month later a tear was discovered at the summit of the bulge, and soft lens material protruded into the anterior chamber. During this time changes in the lens of the left eye made their appearance and at the end of a year the anterior capsule assumed the form of a horseshoe.

W. S. REESE. [ARCH. OPHTH.]

AN UNPIGMENTED PRIMARY TUMOUR OF THE OPTIC DISK. J. P. WHITE and A. LOEWENSTEIN, Brit. J. Ophth. **30**:253 (May) 1946.

The growth was first observed when the boy was 7½ years old. Vision equaled 6/36. The upper two thirds of the disk of the left eye was covered by a whitish, smooth mass of 2 disk diameters. The child was intelligent, well built and well nourished. At the age of 9 years, the disk was covered by a grayish white, oval mass with a smooth surface. The margins of the tumor were tuberous and rose steeply from the fundus (+ 1 D.) to a height of 8 D. A small portion was vascular. The nasal part of the mass was covered by hemorrhages. There was scattered pigment in the lower half of the fundus, with depigmented spots and superficial hemorrhages. The pigment was predominantly in the deeper retinal layers. The fundus of the right eye showed similar changes. Histologic investigation showed a tissue consisting of large, foamy cells, the contents of which were neither fatty nor mucinous. The nature of the regressive process was not determined. The tumor tissue infiltrated the surrounding retina, the posterior layers of which were missing and were perhaps undeveloped. There was a cavernous degeneration in a large part of the optic nerve. The caverns were empty or filled with a fine, foamy substance. A film of subhyaloid blood covered wide areas of the retina. The growth was explained as a phakoma arising from the neuroectodermal cells of the optic stalk, into which the fibers of the retinal ganglion cells grow. As the two layers of the optic stalk consist of potentially pigment-producing cells (the outer layer) and nonpigmented cells (the inner layer), misplacement of either of them may be responsible for the growth of pigmented or nonpigmented phakoma of the disk. The existence of both malformations can be proved. The article is well illustrated.

W. ZENTMAYER. [ARCH. OPHTH.]

REPORT ON A CASE OF HYDROPHTHALMIA (BUPHTHALMOS). E. EPSTEIN, Brit. J. Ophth. **30**:476 (Aug.) 1946.

The case described had many features which might have suggested the diagnosis of megalocornea but it proved to be one of hydrophthalmos. It indicates that the diagnosis of megalocornea in the absence of a familial history can be most difficult and should then be made reservedly.

W. ZENTMAYER. [ARCH. OPHTH.]

ANATOMIC STUDY OF A COMPLEX RETROBULBAR EMBRYONIC MALFORMATION. G. OFFRET, Arch. d'opht. **5**:51, 1945.

This study was prompted by observations at autopsy. The histologic examination presented a complex malformation in the retrobulbar muscle cone, characterized by fragments of malpighian epithelium, glands of the skin and glands of the salivary and mucous type. The author discusses tumors of this type occurring in this area according to the classification of Van Duyse: serous cyst, dermoid cyst and teratoma. Excellent photomicrographs accompany the article, and the author states his belief that the tissue which he has studied lies between a dermoid and a teratoma, since the histologic picture revealed such a multiplicity of different tissues.

L. B. MARLOW. [ARCH. OPHTH.]

IS IT POSSIBLE TO INFLUENCE CONGENITAL COLOR BLINDNESS? E. WOLFFLIN, Ophthalmologica **109**:324 (June) 1945.

The author reviews the work of Studnitz (no references to which are given) on the chemical composition of the material stated to be responsible for the perception of colors. He claims that there are three separate chemical substances,

which have different absorption maxima in the various portions of the spectrum, namely, in the red, yellow and blue regions. These substances are, therefore, known as the red, yellow and blue substances. They are found in slight concentration in retinas containing chiefly cones and have been isolated from the oil droplets in the cones of certain animals. Their chemical nature seems to be that of carotinoids. The red substance is recognized as astaxanthin; the yellow substance, as xanthophyll, and the blue substance, as lacertofulvin. At present, these substances cannot be produced in sufficient quantities to test their effectiveness when supplied to color-blind persons by oral administration, but the author believes that it may be possible to influence color vision by such treatment. No data of any experimental work are given.

F. H. Adler. [Arch. Ophth.]

Light Reflexes Associated with Spherophakia. A. E. Schmid, Ophthalmologica **111**:359 (June) 1946.

A case is reported of so-called dysmorphodystrophia mesodermalis congenita, a type described by Marchesani, in which there were a luxated spherophakic lens in the anterior chamber of one eye and a subluxated lens in the other. It is well known that the normal lens, when dislocated into the anterior chamber, shows under certain conditions of illumination an illuminated line around the entire equator, which is known as the gold edge, or "gold Rand." In the case of the spherophakic lens other reflex streaks besides this equatorial one appear. An illustration is given of these reflex streaks, and the author discusses the origin and nature of the light reflexes in spherophakia and microphakia.

F. H. Adler. [Arch. Ophth.]

Skin Diseases; Allergy

Methods of Local Therapy for Tinea Capitis Due to Microsporon Audouini. Lee Carrick, J. A. M. A., **131**:1189 (Aug. 10) 1946.

A study was made of 171 cases of tinea capitis, of which 169 were due to Microsporon audouini and 2 to Microsporon lonosum, treated with copper oleate ointment, undecylenate-undecylenic acid ointment and propionate-propionic acid ointment. The ages of the children ranged from 1 to 13 years. The ratio of boys to girls was 4.3:1; 62 per cent were white children and 38 per cent were Negro. Careful instructions were given the parents. A soap substitute was usually employed for the shampoos which were needed twice daily.

Seventy-nine patients were sufficiently cooperative to permit evaluation of treatment. Of 17 children using copper oleate ointment, 7 were cured in an average of one hundred and thirty-two days, 2 were moderately improved in one hundred and fifty-eight days and 8 were unimproved in one hundred and seventy-nine days. Of the 25 children using undecylenate-undecylenic acid ointment, 10 were cured in a mean of one hundred and twenty-five days, 8 decidedly improved in one hundred and twenty-seven days, 3 moderately improved in eighty-seven days and 4 unimproved in one hundred and thirty-four days. With propionate-propionic acid ointment, 15 of the 37 children were cured in an average of one hundred and eight days, 7 decidedly improved in one hundred and thirty-three days, 4 moderately improved in one hundred and twenty-five days and 11 unimproved in one hundred and twenty-seven days.

Treatment with these ointments is not a substitute for roentgen ray epilation, but it may be valuable if epilation is not available or practical.

Baird, Wauwatosa, Wis.

TINEA CAPITIS: ITS TREATMENT WITH SPECIAL IODINE AND DILUTE ACETIC ACID. ALBERT STRICKLER, J. A. M. A. **132**:65 (Sept. 14) 1946.

A new type of iodine preparation is described for use in tinea capitis. The iodine is combined with chlorophyll as a catalyst and photosensitizer, dioctyl ester of sodium sulfosuccinic acid ("deceresol") as a wetting agent, magnesium dioxide as a source of oxygen and splenic extract as an enzyme capable of transferring peroxide oxygen. In treatment this preparation was used in combination with 3 per cent solution of acetic acid and heat from an electric light bulb. With these topical applications tinea capitis in 64 per cent of 115 patients was cured.

BAIRD, Wauwatosa, Wis.

PEMPHIGUS, SUCCESSFUL TREATMENT WITH PENICILLIN: REPORT OF A CASE. J. LAMAR CALLAWAY, JAY ARENA, RAY O. NOOJIN and KATHLEEN A. RILEY, J. Pediat. **28**:592 (May) 1946.

Present methods of treatment of pemphigus are so unsatisfactory that any therapeutic agent which brings about a remission or cure is worthy of description. Any conclusion made from the treatment of one patient must necessarily be guarded. We desire to report on the use of penicillin in a patient with proved pemphigus, who experienced a remission, if not a cure, over a two year period of observation.

A 4 year old Jewish girl entered Duke Hospital on Oct. 24, 1943 because of generalized vesicular lesions of one month's duration over the body. The first bullous lesion had been noted on the left knee. The mother opened the bulla and treated it locally with sulfathiazole ointment. Three days later the child was taken to her physician and a diagnosis of impetigo was made. She was given ultraviolet therapy on the fourth, fifth and seventh days, despite which the lesions continued to spread over the body. At this time the mother noticed some new papular and bullous lesions. One week after onset, the patient was seen, in consultation, by a dermatologist who advised sulfathiazole orally and the application of 10 per cent ammoniated mercury locally. The sulfathiazole was discontinued in twenty-four hours because of nausea. On the ninth day after onset, numerous new bullae appeared, which were preceded by an erythematous papular eruption. Various calamine preparations were used to allay the pruritus. The lesions continued to spread. Three weeks after onset she was seen, in consultation, by another dermatologist, who confirmed the diagnosis of bullous impetigo. Therapy at this time consisted in removal of the crusts with soap and water, followed by applications of a mercurial ointment. New bullae appeared daily in spite of therapy, and four weeks after onset the body was almost entirely covered with new and old lesions.

Physical examination revealed nothing abnormal except the skin lesions. Results of routine laboratory studies were normal. Patch tests with 20 and 50 per cent potassium iodide gave negative results. A biopsy of the skin showed conditions compatible with pemphigus. The result of the phytopharmacologic test was 71 per cent (normal). Cultures from the crusted lesions showed hemolytic Staphylococcus aureus and beta hemolytic streptococci.

On admission to the hospital the patient was given 1:4,000 potassium permanganate baths, 1 per cent gentian violet solution and 5 per cent ammoniated mercury in "creamalin" (an antacid containing aluminum hydroxide gel). She was also given a course of sulfathiazole, consisting of 0.5 Gm. every four hours for six days. There was no improvement.

One week later she was given a course of "naphuride sodium" (suramin sodium), consisting of 0.5 Gm. every day for three days, without improvement.

Three days after the last dose of suramin sodium, she was given 10,000 units of penicillin intravenously. The following day she was started on a course of

penicillin administered intramuscularly, during which she received 5,000 units every three hours, or a total dosage of 116,000 units. During the course of penicillin, the temperature spiked from 38 to 39.5 C. (100.4 to 103.1 F.). She improved within one week and was discharged one month from the date of admission. At discharge, there were no new bullae, the old lesions were almost completely healed, and the patient was in good health generally.

Two years after discharge the patient was in excellent health and had developed normally, both mentally and physically. There had been no recurrence of the eruption. No conclusions can be drawn from a single instance, but in a patient with a disease as serious as pemphigus, trial with peniclilin seems indicated.

AUTHORS' ABSTRACT.

PRESSURES REQUIRED TO PRODUCE INTRADERMAL WHEALS IN NORMAL HUMAN SUBJECTS. W. G. MOSS and C. C. PFEIFFER, Proc. Soc. Exper. Biol. & Med. **63**:44 (Oct.) 1946.

Wheals were raised in the lower part of the forearm of 11 subjects, using a 27 gage needle and a tuberculin syringe, which was also connected with a mercury manometer recording optically. Five measurements were made serially on the 11 subjects. Considerable variation was found in consecutive readings, probably owing to the depth of the needle tip. Measurements made with the bevel of the needle inserted up toward the epidermis were consistently higher than with the bevel pointed down. The pressure required to produce intradermal wheals in normal persons varied from 1,000 to 32,000 mm. of mercury, with a mean pressure of about 2,000 mm. of mercury. The wheal-producing action of histamine was apparently too slow to lower the pressure required to produce wheals. The authors also conclude: "No consistent differences in wheal pressures were found between males and females, or among Whites, Negroes and Japanese."

HANSEN, Galveston, Texas.

TWO CASES OF EHLERS-DANLOS SYNDROME. F. L. KING-LEWIS, Proc. Roy. Soc. Med. **39**:135 (Jan.) 1946.

Two cases of Ehlers-Danlos syndrome are reported, one in a boy 3½ years of age and the other in a girl aged 9 years.

WILLIAMSON, New Orleans.

Surgery and Orthopedics

PENICILLIN AND OTHER ANTIBIOTICS AS CHEMOTHERAPEUTIC AGENTS IN WOUND INFECTIONS. ERWIN NETER, New York State J. Med. **45**:1982 (Sept. 15) 1945.

While penicillin is of inestimable value in the prevention and treatment of wound infections, it and other chemotherapeutic agents have their limits and cannot replace medical and surgical therapy.

A good review of the literature on the subject up to September 1945 is given.

AIKMAN, Rochester, N. Y.

ADVISORY CENTER AND INSTITUTE FOR PREVENTIVE PHYSICAL EXERCISES. JOSEF SVEJCAR, Pediat. listy **1**:140, 1946.

The author discusses the purpose and aim of the advisory center and institute for preventive physical exercises, which are meant for those children who are unable to attend the ordinary gymnastic classes at school, but who are not yet in need of orthopedic exercises.

FROM THE AUTHOR'S SUMMARY.

Teeth and Dentistry

DENTAL FLUOROSIS. H. SAINSBURY, Arch. Dis. Childhood **21**:115 (June) 1946.

The main features of a series of cases of dental fluorosis are described as they were presented among the children of a small village.

The appearance of "brownin" is the most striking and certain indication of the presence of the condition. It was this appearance which attracted the attention of Ainsworth (1933) in England. "Brownin" closely resembles tobacco staining, but among children, in whom it develops slowly, the pigment is confined to the outer surface of the upper teeth.

Of the lesions noted (pitting, mottling, chalk patches and "brownin"), only the last can be produced by fluorosis alone. Factors in differential diagnosis are given in the case of the other lesions, and it is to be noted that the coexistence of acute infections and nutritional defects in infancy renders the precise estimation of the amount of fluorosis prevailing in a locality difficult. The lesions occur on the permanent teeth only. No evidence of osteoarthritis was observed among the children.

The incidence of dental caries was low (2.7 per cent). Endemic goiter was present in the district. Clinical findings were confirmed by demonstrating the presence of fluorine to the extent of 7 parts per million in the water.

KELLY, Milwaukee.

THE RESPONSIBILITY OF THE PEDIATRICIAN IN THE ORTHODONTIC PROBLEM. FRANCIS M. POTTENGER JR., California Med. **65**:169 (Oct.) 1946.

The pediatrician should assume a double trust in the health guidance of an infant, according to Dr. Pottenger. Not only does the pediatrician treat the infant for infectious diseases and prescribe a diet to meet its growing needs, but also he should direct a program calculated to determine the future dental development of the child.

He can determine by routine roentgenograms the changing conditions of the skull and can interpret these findings as prophecies of future requirement for orthodontic treatment. By encouraging the mother to nurse the infant, the pediatrician can early help the child to develop strong faciodental structures, entirely different from those of the bottle-fed baby. He can avert or lessen many a dental deformity by recognizing early hypogonad, hypothyroid and other endocrine disturbances of children and by instituting the proper therapy, which, in turn, improves the faciodental structures. He can also obviate many serious dental problems by checking allergies as quickly as possible, since the continual insult of an allergic process has concomitant dental problems. The pediatrician, by means of roentgenograms taken at regular intervals, should anticipate the future development of orthodontic problems so that the orthodontist may be consulted at an early date, before the permanent teeth have erupted.

PRYOR, Redwood City, Calif.

Miscellaneous

TRENDS IN THE AGE DISTRIBUTION OF CHILDHOOD DISEASES. ELMER M. BINGHAM, California Med. **65**:225 (Nov.) 1946.

Bingham classifies childhood diseases as follows: (1) those which every person must expect to have at some time during his life—pertussis, measles, chickenpox, rubella and mumps; (2) those which he may acquire but for which

specific artificial immunity is available—diphtheria and smallpox, and (3) those which he may acquire but for which there is no specific protection—poliomyelitis and scarlet fever.

Analysis of the age distribution of childhood diseases in San Joaquin County for the years 1925 to 1944 shows the following trends: chickenpox, a steady increase in incidence in preschool children and a corresponding decrease in children of school age; measles, pertussis and scarlet fever, an increased incidence in preschool children, but not one so distinct or so regular as that for chickenpox; mumps and rubella, an increase in incidence in persons over 10 years old; diphtheria, a definite shift away from the two younger age groups, but an increase in total cases and cases in children over 5, and smallpox and poliomyelitis, a shift to the older age groups.

The advisability of sponsored and controlled epidemics of some of the contagious diseases is discussed. Bingham summarizes the reasons for changes in the age distribution, as follows: (*a*) increased protection or increased exposure of certain age groups; (*b*) a change in the number of susceptible persons within an age group by an increasing birth rate or migration of population, and/or (*c*) improved reporting of cases occurring within a specific age group.

For those diseases which have shown an increase in the total number of cases, protection of children does not appear to have been a factor in changing the age distribution.

If efforts to protect the child from the common virus diseases of childhood are ineffectual, they should be modified with prevention of complications and mortality as an objective.

It should be seen that the infant is immunized against pertussis, diphtheria and smallpox, and that the young child has modified measles; chickenpox may be allowed to come when it will; one may hope that mumps comes before puberty and rubella any time before pregnancy, and the protection against smallpox and diphtheria should be prolonged as long as possible.

PRYOR, Redwood City, Calif.

RECENT PROGRESS IN PEDIATRICS. PETER COHEN, California Med. **66**:30 (Jan.) 1947.

Cohen reviewed articles on pediatrics of practical value and interest to the general practitioner which had been published in the preceding two years. The subjects covered include treatment of pneumococcic meningitis with penicillin and sulfonamide compounds, treatment of influenzal meningitis with streptomycin, treatment of tuberculous meningitis with streptomycin, relationship of antepartum rubella and congenital defects, chemoprophylaxis against rheumatic fever with sulfonamide drugs, treatment of megaloblastic anemia with pteroyl glutamic acid, surgical treatment of congenital heart disease, recent trends in the treatment of convulsive disorders and the antihistaminic agents.

PRYOR, Redwood City, Calif.

Directory of Pediatric Societies *

INTERNATIONAL

Sixth International Congress of Pediatrics

President: Prof. Guido Fanconi.
Secretary: Dr. H. Zellweger, Kinderklinik, Zurich.
American Committee:
President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: Zurich, Switzerland. Time: July 24-28, 1950.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quay Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

Asociación Pediatrica de Guatemala

President: Dr. Carlos Manuel Monzon, Plazuela Santuario de Guadalupe, Guadalupe.
Secretary: Dr. Maria Isabel Escobar, Casa del Niño no. 1, Guadalupe.

British Paediatric Society

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Bulgarian Pediatric Society

President: Dr. L. Ratchew, University Children's Hospital, Wassil Kolarow 46, Sofia.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

Czechoslovak Pediatric Society

Chairman: Prof. Dr. Jiri Brdlík, 2 Sokolská, Prague II.

Danish Pediatric Society

Chairman: Prof. Preben Plum.
Secretary: Dr. Elin Fog, Søllingsvey 17, Charlottenlund, Denmark.

German Pediatric Society

President: Dr. H. Kleinschmidt.
Secretary: Dr. F. Goebel, 5 Moorenstrasse, Düsseldorf, Germany (British Zone).
Place: Düsseldorf. Time: September 1949.

Hellenic Society of Pediatrics

President: Dr. C. Saroglou, Patission St. 74, Athens, Greece.
Secretary-General: Dr. S. Charocopos, Alexandras Ave. 1, Athens, Greece.

Indian Pediatric Society

President: Dr. K. C. Chaudhuri, 56/2 Creek Row, Calcutta 13.
Secretary: Dr. N. G. Mojumdar, 148 Russa Rd., Calcutta 26.
Place: 67 Dharamtala St., Calcutta 13. Time: Every second and fourth Wednesday of each month.

Nederlandsche Vereeninging voor Kindergeneeskunde

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicans of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Pediatric Society of New Zealand

President: Dr. Lawrence Ludbrook, The Lister Building, Victoria Street East, Auckland.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft für Pädiatrie

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

Sociedad Boliviana de Pediatria

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela D., Casilla 272, La Paz, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedad Chilena de Pediatria

President: Mr. Raúl Matte, Santiago, Chile.
General Secretary: Dr. Mariano Latorre, Santiago, Chile.
Place: Medical Society, Santiago, Chile. Time: 7:30 p. m., weekly.

SOCIEDAD CUBANA DE PEDIATRIA

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

SOCIEDAD ECUATORIANA DE PEDIATRIA

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDADE PORTUGUÊSA DE PEDIATRIA

President: Prof. Almeida Garrett.
Secretary-Generale: Dr. Cordeiro Ferreira, Hospital de D. Estefania, Lisbon.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Guillermo Flores, Chacin, Sur 17, no. 26-2, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SOCIETÉ POLONAISE DE PÉDIATRIE

President: Dr. Jan Bogdanowicz, Dzialdowska 1, Warsaw.
Secretary: Dr. Zofia Leimbach, Mieroslawskiego 9 m.6, Warsaw.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH ASSOCIATION OF PEDIATRICS

President: Prof. A. Lichtenstein, Crown Princess Louise's Children's Hospital, 30 Polhemsgata, Stockholm.
Secretary: Dr. K. A. Melin, Farjestadsvägen 16, Ängby.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.
Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCETY OF PEDIATRICS

President: Dr. Héctor C. Bazzano.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo.

VIENNA PEDIATRIC SOCIETY

President: Prof. Dr. A. Solé, Karolinen-Kinderspital, Sobieskigasse 31, Vienna 9.
Secretary: Doz. Dr. Asperger, Universitäts-Kinderklinik, Lazarettgasse 14, Vienna 9.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston 15.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Annual Meeting: Place: San Francisco. Time: Nov. 14-17, 1949.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Francis F. Schwentker, 601 N. Broadway, Baltimore, Md.
Secretary-Treasurer: Dr. Robert Ward, Bellevue Hospital, New York 16.
Place: French Lick, Ind. Time: 1950.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

Northwestern Pediatric Society

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. William D. Rothwell Jr., Republic Bldg., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

STATE

Alabama Pediatric Society

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.
Place: Montgomery, Ala. Time: September 1949.

Arizona Pediatric Society

President: Dr. Carl A. Holmes, 1401 N. 7th Ave., Phoenix.
Secretary-Treasurer: Jacob M. Sobol, 607 Heard Bldg., Phoenix.
Place: Phoenix or Tucson. Time: On call.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.

Florida State Pediatric Society

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SOCIETY

Chairman: Dr. Thurman B. Givan, 115 Remsen St., Brooklyn 2.
Secretary: Dr. Reginald A. Higgons, Port Chester.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. George Clark, 1817 Vinton St., Omaha.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. Thomas B. Walker, Porthmouth.
Secretary-Treasurer: Dr. Ursula G. Sanders, Concord.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.
Secretary: Dr. N. T. Crane, 147 E. 7th St., Plainfield, N. J.

NEW MEXICO STATE PEDIATRIC SOCIETY

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. S. S. Saunders, High Point, N. C.
Secretary: Dr. S. C. Dees, Durham, N. C.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

NORTH DAKOTA PEDIATRIC SOCIETY

President: Dr. R. E. Dyson, Northwest Clinic, Minot, N. D.
Secretary-Treasurer: Dr. William J. Ball, Northwest Clinic, Minot, N. D.
Place: Fargo Clinic, Fargo, N. D. Time: October 15.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

PHILIPPINE PEDIATRIC SOCIETY

President: Dr. Alberto V. Tupas, Philippine General Hospital, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Philippine General Hospital, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

TENNESSEE PEDIATRIC SOCIETY

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

TEXAS PEDIATRIC SOCIETY

President: Dr. John K. Glen, 4412 Montrose St., Houston.
Secretary-Treasurer: Dr. James N. Walker, 3616 Tulsa Way, Fort Worth 7.
Place: San Antonio. Time: Oct. 7-8, 1949.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. C. P. Brown, 142 W. York St., Norfolk.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

WISCONSIN STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

BRONX PEDIATRIC SOCIETY

President: Dr. Nathan M. Greenstein, 1488 Metropolitan Ave., New York.
Secretary: Dr. George Weiss, 790 Grand Concourse, New York 51.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Walter R. Coles, 604-2d St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. Arthur F. Abt, 104 S. Michigan Blvd., Chicago 3.
Secretary: Dr. Alfred S. Traisman, 6349 N. Clark St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

Detroit Pediatric Society

President: Dr. Wilfred D. H. Nolting, 16840 E. Warren, Detroit.
Secretary: Dr. Ruben Meyer, 938 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

Fort Worth Pediatric Society

President: Dr. Frank Cohen, 712 S. Henderson, Fort Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania, Fort Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

Honolulu Pediatric Society

President: Dr. Donald Marshall, Medical Group, Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu

Houston Pediatric Society

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville-Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Samuel Silber, 865 Park Place, Brooklyn.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. James Conway, 1721 E. Lake Bluff Blvd., Milwaukee 11, Wis.
Secretary-Treasurer: Dr. Walter Polacheck, 425 E. Wisconsin Ave., Milwaukee 2, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. John M. Lee, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Dan S. Sanders Jr., 2103 Hayes St., Nashville, Tenn.
Time: Third Thursday of every month.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103rd St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Aims C. McGuinness, 1740 Bainbridge St., Philadelphia 46.
Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.
Place: College of Physicians, 19 S. 22nd St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. J. A. Gilmartin, 3708–15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

QUEENS PEDIATRIC SOCIETY

President: Dr. Henry A. Reisman, 88-03 146th St., Jamaica, L. I
Secretary: Dr. Moe Goldstein III, 3a 76th Ave., Forest Hills, L. I.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Merl J. Carson, 500 S. Kingshighway, St. Louis.
Secretary-Treasurer: Dr. Jackson K. Eto, 734 Missouri Theatre Bldg., St. Louis 3.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

SAN ANTONIO PEDIATRIC SOCIETY

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Chester I. Mead, 1930 Truxton Ave., Bakersfield, Calif.
Secretary: Dr. Clement H. Maloney, 416 N. Bedford Dr., Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

WACO PEDIATRIC SOCIETY

President: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.
Secretary: Dr. F. W. Hoehn, 1422 Austin Ave., Waco, Texas.
Place: Provident Hospital, 1725 Colcord, Waco, Texas. Time: Third Thursday of each month.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRICS SECTION (NEW YORK)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).

WICHITA PEDIATRIC SOCIETY

President: Dr. Walter L. Schafer, 401 N. Emporia St., Wichita 2, Kan.
Secretary: Dr. William F. McGuire, 401 N. Emporia St., Wichita 2, Kan.
Place: Variable. Time: First Thursday of each month.